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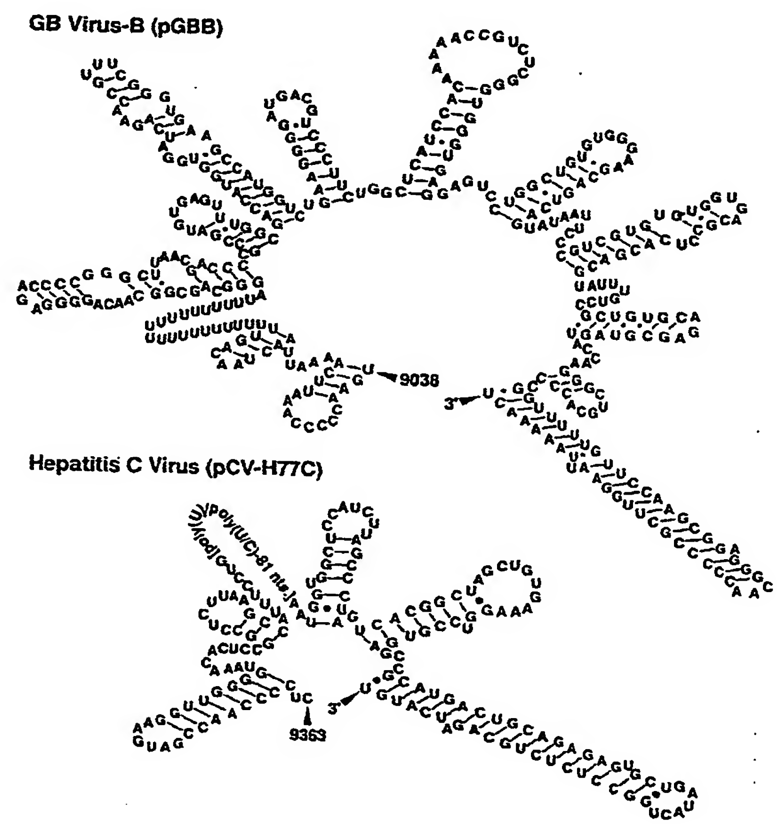
(54) Title: INFECTIOUS cDNA CLONE OF GB VIRUS B AND USES THEREOF



(57) Abstract: The present invention relates to nucleic acid sequence which comprises the genome of an infectious GB virus B clone. The invention also relates to the use of the nucleic acid sequence of the infectious GB virus B clone to indirectly study the molecular properties of HCV, and in the production of HCV/GBV-B chimeras. The invention further relates to the use of the infectious nucleic acid sequence of GB virus B clone and the HCV/GBV-B chimeras in the development of vaccines and therapeutics for HCV.

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Title of Invention

Infectious cDNA clone of GB Virus B and Uses Thereof

Field of Invention

The present invention relates to nucleic acid sequence which comprises the genome of an infectious GB virus B (GBV-B) clone. The invention also relates to the use of the nucleic acid sequence of the infectious GB virus B clone to study indirectly the molecular properties of hepatitis C virus (HCV), and in the production of HCV/GBV-B chimeras. The invention further relates to the use of the infectious nucleic acid sequence of the GB virus B clone and the HCV/GBV-B chimeras in the development of vaccines and therapeutics for HCV.

Background of Invention

Transmission studies of potential human hepatitis agents were first reported in 1967 (Deinhardt 1967). Four tamarins inoculated with acute phase sera from a surgeon with acute hepatitis (patient GB) developed hepatitis, as did most tamarins inoculated in serial passage studies. Subsequent studies indicated that the etiological agent responsible for the development of hepatitis in these animals was not any of the known human hepatitis viruses (Purcell 1994). In 1995, two related RNA viruses named GB virus-B (GBV-B) and GB virus A (GBV-A) were identified in acute phase sera of a tamarin which developed hepatitis following inoculation with serum of the eleventh tamarin passage of the putative GB agent (Simons 1995a).

GBV-B infection of tamarins resulted in acute resolving hepatitis (Schlauder 1995, Buhk 1997). The

natural host of GBV-B is still unknown as the virus has not been detected in uninoculated animals or in humans.

GBV-A, on the other hand, is an indigenous tamarin virus rather than a component of the original GB inoculum (Bukh 1997, Erker 1998). Experimental infection of tamarins with GBV-A did not produce hepatitis (Schlauder 1995). A human agent, GBV-C or hepatitis G virus, most closely related to GBV-A, was later identified (Simons 1995b, Linnen 1996). However, it is still not clear whether this virus actually causes hepatitis (Alter 1998, Bukh 1998a). Thus, of the known GB viruses, GBV-B may be the only true hepatitis virus.

Based on analysis of their genomic sequences, GBV-A, GBV-B and GBV-C were classified as members of the *Flaviviridae* family of viruses, and among the known viruses, GBV-B is the virus most closely related to hepatitis C virus (HCV) (Muerhoff 1995, Robertson 1998).

The GBV-B virus contains a positive-sense, single-stranded RNA genome of 9143 nucleotides (nts) (Simons 1995a, Muerhoff 1995). The viral genome of GBV-B consists of a 5′ untranslated region (UTR), a single long open reading frame (ORF) and a 3′ UTR. Based on known motifs, structural proteins were predicted to be encoded in the 5' portion of the ORF and nonstructural (NS) proteins in the 3' portion of the ORF (Muerhoff 1995). The hydropathy plots of the polyproteins of GBV-B and HCV are very similar even though the overall homology of the predicted polyproteins between GBV-B and HCV is only about 25-30% (Muerhoff 1995). The putative envelope proteins (E1 and E2) of GBV-B and HCV share common structural features, and significant homology was observed between the NS3 serine protease, the NS3 RNA

helicase, and the NS5 RNA-dependent RNA polymerase regions of GBV-B and HCV (Muerhoff 1995). Furthermore, the function and substrate specificity of the GBV-B and HCV NS3 serine proteases are also similar (Scarselli 1997). The genomic structure and organization of GBV-B and HCV share additional features of interest. First, colinear regions with significant sequence homology were identified in the 5' UTRs (Muerhoff 1995) and the predicted IRES structure of GBV-B is similar to that of HCV (Lemon 1997). Second, both viruses begin the 3' UTR with a short sequence followed by a poly (U) stretch followed by additional nucleotides (50 nucleotides for GBV-B and 98 nucleotides for HCV). However, the 3' terminal sequence of HCV forms a stable stem-loop structure (Kolykhalov 1996) whereas the published 3' terminal sequence of GBV-B does not.

To date, molecular studies of HCV are severely limited by the lack of an efficient cell culture system for the virus and by expense and limited availability of chimpanzees, the sole animal model for HCV. Accordingly, a less expensive and more readily available animal than chimpanzees is necessary as an animal model for the study of HCV.

Summary of Invention

The present invention relates to nucleic acid sequence which comprises the genome of an infectious GB virus B (GBV-B) clone. It is therefore an object of the invention to provide nucleic acid sequence which encodes an infectious GBV-B. Such nucleic acid sequence is referred to throughout the application as "infectious nucleic acid sequence".

As significant structural homology exists between the genomes of GBV-B and HCV, the invention also relates to the use of infection of tamarins with the infectious nucleic acid sequence of GBV-B or with mutants of the infectious sequence to study indirectly the molecular properties of hepatitis C virus (HCV) or as a preliminary screen to identify agents which have antiviral activity against HCV.

The invention further relates to "chimeric nucleic acid sequences" consisting of portions of the infectious nucleic acid sequence of GBV-B and portions of the nucleic acid sequences of other viruses closely related to GBV-B such as HCV, GBV-C or other members of the *Flaviviridae* family which do not replicate in tamarins. In a preferred embodiment, the chimeric nucleic acid sequences consist of portions of the infectious nucleic acid sequence of GBV-B and portions of the nucleic acid sequence of HCV. The nucleic acid sequences taken from GBV-B and HCV can be open-reading frame sequences, and/or sequences from the 5'UTR and/or 3'UTR.

In one embodiment, GBV-B/HCV chimeras may be made in which 5' or 3' UTR sequences of the GBV-B infectious clone are replaced with the corresponding sequence from an HCV clone.

In another embodiment, GBV-B/HCV chimeras may be constructed in which the structural or non-structural regions of GBV-B are replaced by corresponding regions of HCV. Thus, such a chimera would contain, for example, the HCV structual region in a GBV-B "genomic backbone". Of course, it is understood by one of skill in the art that the construction of the above-described

chimeric nucleic acid sequences may be reversed such that, for example, the GBV structural region may replace the structual region of an HCV genome to produce a chimera in which the GBV structural region is contained in an HCV backbone.

The invention further relates to the use of the chimeric nucleic acid sequences of the invention to study the functions of HCV genes, and for the development of vaccine and antiviral agents against HCV.

The invention also relates to the use of the infectious GBV-B nucleic acid sequence, the mutated GBV-B nucleic acid sequences or the chimeric sequences of the invention to identify cell lines capable of supporting the replication of GBV-B or the chimeras of the invention.

The present invention also relates to the polypeptides encoded by the nucleic acid sequences of the invention or fragments thereof.

The present invention further relates to the in vitro and in vivo production of GBV-B, mutant GBV-B viruses or chimeric GBV-B/HCV viruses from the nucleic acid sequences of the invention.

The invention also provides that the nucleic acid sequences and viruses of the invention be supplied in the form of a kit, alone or in the form of a pharmaceutical composition.

Brief Description Of Figures

Figure 1 shows a flow diagram of GB virus transmission studies in two species of tamarins, *Saguinus mystax* (SM) and *Saguinus oedipus* (SO). The animals infected with GBV-B (Simons 1995a) are boxed.

Two serum pools (GB 8/93 and GB 2/94) were made from acutely infected animals. Both pools contained GBV-B, as well as GBV-A (Simons 1995) at a titer of 10^8 genome equivalent (GE)/ml. A 10% liver homogenate (CT 11/91) was made from a sacrificed tamarin. A number of *S. mystax* tamarins (SM 737, 749, 750, 760, 782, 795 and 799) and *S. oedipus* tamarins (SO 100) were naturally infected with GBV-A_{SM} and GBV-A_{SO}, respectively, prior to inoculation (Bukh 1997). Only two tamarins (SM 720 and 748), both GBV-A_{SM} negative, became infected with GBV-A (Simons 1995) following inoculation. Tamarins SM42 and SM670 were not tested for GBV-A or GBV-A_{SM}.

Figure 2 shows the course of GBV-B infection in tamarins (*S. mystax*) inoculated with a dilution series of the GB 2/94 pool. All animals were inoculated intravenously at week 0 with 1 ml of the indicated dilution. Results of qualitative RT-nested PCR for GBV-B in serum are shown at the top (filled circles, positive; empty circles, negative). Serum levels of isocitrate dehydrogenase (ICD in units/ml); shaded area) and the estimated $\log_{10}$ GBV-B GE titer (vertical columns) were plotted against time.

Figure 3 shows alignment of the 3' UTR sequences of GBV-B. The sequence of the infectious clone of GBV-B (pGBB) is shown at the top (nts. 9038-9399). The other sequences shown are: pGBB5-1, a non-infectious clone of GBV-B; GBV-B, a prototype of GBV-B (Simons 1995); eleven "gb" clones obtained from CT 11/91 liver homogenate by 5' RACE on the minus-strand GBV-B RNA; four "29" clones obtained from GB 2/94 pool by RT-PCR across 5'-to-3'-end-ligated viral GBV-B RNA; and seven "GBB3" clones obtained from GB 2/94 pool by standard RT-PCR.

With pGBB as the reference, nucleotide substitutions or insertions are shown as uppercase letters, identical nucleotides are shown as dots and nucleotide deletions are shown as dashes.

Figure 4 shows the predicted secondary structure of the 3' UTRs of GBV-B and HCV as determined by the program "mfold" (Genetics Computer Group).

Figure 5 shows the course of GBV-B infection in *S. mystax* tamarins transfected with RNA transcripts of pGBB. Both animals were negative for GBV-A_{SM}. At week 0 transcription mixtures were injected into tamarins by percutaneous intrahepatic injection guided by ultrasound. Results of qualitative RT-nested PCR for GBV-B in serum is shown at the top (filled circles, positive; empty circles, negative). Serum levels of isocitrate dehydrogenase (ICD in units/ml; shaded area) and the estimated $\log_{10}$ GBV-B GE titer (vertical columns) were plotted against time.

Figures 6A-6F show the nucleotide sequence of the infectious hepatitis C virus clone of genotype 1a strain H77C and Figures 6G-6H show the amino acid sequence encoded by the clone.

Figures 7A-7F show the nucleotide sequence of the infectious hepatitis C virus clone of genotype 1b strain HC-J4 and Figures 7G-H show the amino acid sequence encoded by the clone.

Description of The Invention

The present invention relates to nucleic acid sequence which comprises the genome of an infectious GB virus B (GBV-B) clone. The nucleic acid sequence which comprises the genome of an infectious GBV-B virus is

shown in SEQ ID NO:1 and is contained in the plasmid construct pGBB deposited with the American Type Culture Collection (ATCC) on May 28, 1999 and having ATCC accession number PTA-152. The present invention relates to the identification of a 260 nucleotide sequence at the 3' end of the infectious GBV-B clone which is shown in Example 3 to be necessary for the development of the infectious clone.

Since GBV-B is the virus most closely related to HCV, the present invention also relates to experimental infection of tamarins with the infectious GBV-B clone of the invention or with mutants of the infectious GBV clone to study indirectly the molecular properties of HCV or as a preliminary screen to identify agents which have antiviral activity against HCV. For example, since the predicted internal ribosome entry site (IRES) structure in the 5'UTR of GBV-B is similar to that of HCV (Lemon 1997), the NS3 serine proteases of GBV-B and HCV have been shown to share substrate specificity _in vitro_ (Scarselli 1997), and the 3'UTRs of HCV (Yanagi 1999) and GBV-B (see Examples) have been shown to be critical for viral infectivity, mutagenesis of these regions in the GBV-B infectious clone may be undertaken to examine IRES function, NS3 serine protease activity or the role of the 3'UTR in viral infectivity _in vivo_. Where such "mutations" are introduced into the GBV-B clone of the invention to create a "mutated" GBV-B sequence, the mutations include, but are not limited to, point mutations, deletions and insertions. Of course, one of ordinary skill in the art would recognize that the size of the insertions would be limited by the ability of the resultant nucleic acid sequence to be

properly packaged within the virion. Such mutations could be produced by techniques known to those of skill in the art such as site-directed mutagenesis, fusion PCR, and restriction digestion followed by religation.

Alternatively, given the significant structural homology that exists between the genomes of GBV and HCV, the infectious GBV-B clone may be used to screen for inhibitors of IRES function or viral enzyme activity (for example, NS3 helicase, NS3 protease, NS2-NS3 protease or NS5B RNA polymerase activity). Such inhibitors may be useful as antiviral agents to HCV since viral enzyme activity and IRES function are known to be critical for HCV replication.

The effect of such inhibitors on the IRES function or viral activity of the GBV-B encoded by the infectious sequence of the invention may be measured by assays known to those of skill in the art to measure directly or indirectly viral replication or viral pathogenicity. Such assays include, but are not limited to, the measurement of virus titer in serum or liver of an infected tamarin by PCR or the measurement of GBV-B viral protein expression in liver cells of an infected tamarin by immunoflourescence or Western blot. Of course, it is understood that a comparison of results obtained for control tamarins (treated only with infectious nucleic acid sequence) with those obtained for treated tamarins (nucleic acid sequence and antiviral agent) would indicate, the degree, if any, of antiviral activity of the candidate antiviral agent. Of course, one of ordinary skill in the art would readily understand that the tamarins can be treated with the candidate antiviral agent either before or after

exposure to the infectious nucleic acid sequence of the present invention.

In yet another embodiment, the invention relates to "chimeric nucleic acid sequences" which consist of portions of the infectious nucleic acid sequence of GBV-B and portions of nucleic acid sequences of viruses which are related to GBV-B such as HCV, GBV-C and other members of the Flaviviridae family which do not infect tamarins. In a preferred embodiment, chimeric nucleic acid sequences consist of portions of the infectious nucleic acid sequence of GBV-B and portions of nucleic acid sequences of hepatitis C viruses (HCV) of various genotypes or subtypes; preferably portions of nucleic acid sequence of infectious HCV clones of genotypes 1a (ATCC accession number PTA-157; Figures 6A-6F), 1b (ATCC accession number 209596; Figures 7A-7F) or 2a (ATCC accession number PTA-153; SEQ ID NO: 4). The nucleic acid sequences taken from GBV-B and HCV can be open-reading frame sequences, and/or sequences from the 5'UTR and/or 3'UTR. The gene borders of the HCV genome, including nucleotide and amino acid locations, have been determined, for example, as depicted in Houghton, M. (1996), and the putative gene borders of the GBV-B are shown in Table 1.

Of course, it is understood that the production of GBV-B/HCV chimeras could include insertion of specific genes or regions of the infectious GBV-B clone into an HCV "genomic backbone" (where the HCV genomic backbone is preferably an infectious nucleic acid sequence of HCV genotypes 1a, 1b or 2a described above) or alternatively, could include insertion of

specific genes (or portions thereof) or regions of an HCV genome into the GBV-B infectious clone of the invention. Of course, where HCV genes or regions are to be inserted into the GBV-B infectious clone, it is to be understood that the inserted HCV sequences may be unmodified or may be mutated in order to examine the effect of the mutation(s) on the function of the inserted HCV gene or region in the chimeric GBV-B-HCV virus.

Such chimeras can readily be produced by methods known to those of ordinary skill in the art.

In one embodiment, GBV-B/HCV chimeras may be made in which 5' or 3' UTR sequences of the GBV-B infectious clone are replaced with the corresponding sequence from an HCV clone. For example, chimeras may be constructed in which the IRES sequence of the infectious GBV-B clone is replaced by the IRES sequence of HCV. Such chimeras can be used in identifying inhibitors of IRES activity which would be useful as antiviral agents, or could be used to examine HCV IRES function <u>in vivo</u>. Alternatively, mutations could be introduced into the HCV IRES contained in the GBV-B clone in order to examine the effect of the mutation(s) on IRES function <u>in vivo</u>.

Alternatively, GBV-B/HCV chimeras may be made in which the 3'UTR sequence of GBV-B is replaced by the 3'UTR sequence of HCV. As the 3' terminal stem-loop structure is believed to be important for initiation of RNA replication and has been shown to be critical for infectivity of HCV <u>in vivo</u>, such chimeras may be used for more detailed analysis of the function of the 3' UTR

sequence of HCV *in vivo* and for the testing of candidate antiviral agents.

In another embodiment, GBV-B/HCV chimeras may be constructed in which the structural or non-structural regions of GBV-B are replaced by corresponding regions of HCV. Such chimeras would be useful in identifying whether the inability of HCV to infect tamarins is due to the inability of HCV's structural region to bind the receptor necessary for infection of tamarins or to the absence of sequences in HCV's nonstructural regions which are necessary for replication in tamarins. For example, the ability to infect tamarins with GBV-B/HCV chimeras in which the non-structural region of GBV-B is replaced by the non-structural region of HCV would indicate that the structural genes of GBV-B are necessary for viral infection in tamarins, and that the inability of HCV to infect tamarins is likely due to its lack of receptors for HCV.

Alternatively, the ability to infect tamarins with GBV-B/HCV chimeras in which the structural region of GBV-B is replaced by the structural region of HCV would indicate that the non-structural genes of GBV-B are critical for viral infection in tamarins, and that the inability of HCV to infect tamarins is likely due to HCV's lack of nonstructural sequences which are necessary for replication in tamarins.

Of course, GBV-B-HCV chimeras may be constructed in which only a portion of the non-structural or structural regions of GBV-B are replaced by the corresponding portions of HCV sequences. For example, a chimera in which only one or two of the three structural genes (C, E1 and E2) of GBV-B are replaced by

the corresponding HCV structural genes may be made. In one embodiment, nucleic acid sequences comprising the E1 and E2 genes of GBV-B may be replaced by the sequences comprising the HCV E1 and E2 genes. In another embodiment, nucleic acid sequence comprising either the E1 or E2 gene of GBV-B is replaced by sequence encoding either the HCV E1 or E2 gene.

Alternatively, only a fragment of a GBV-B structural gene in the infectious GBV clone may be replaced with the corresponding HCV gene fragments. For example, the amino terminal of the GBV-B E1 gene may be replaced by the corresponding portion of an HCV E1 gene or an amino terminal portion of the GBV-B E2 gene may be replaced by an amino terminal portion of HCV E2 gene tht containing the HVR1 region. As the structural genes of HCV are believed to be important for neutralization, chimeras containing an HCV structural gene(s) or fragment(s) thereof can be used to develop vaccines against HCV.

In yet another embodiment, chimeras in which individual non-structural genes of GBV-B, such as NS3 RNA helicase, NS3 protease, or the NS5B RNA-dependent RNA polymerase are replaced by the corresponding non-structural genes of HCV may be constructed. Such chimeras would, for example, be useful in identifying inhibitors of viral enzyme activity which would be useful as antiviral agents. Of course, it is understood that in order to construct chimeras in which the polyprotein cleavage sites of the GBV-B remain intact, it may be desirable to replace only a fragment of a nonstructural gene of GBV-B with the corresponding HCV gene fragment.

The present invention also relates to polypeptides encoded by the nucleic acid sequences of the invention or fragments thereof. In one embodiment, said polypeptide or polypeptides may be fully or partially purified from viruses produced by cells transfected with the nucleic acid sequences of the invention. In another embodiment, the polypeptide or polypeptides may be produced recombinantly from a fragment of the nucleic acid sequences of the invention. In yet another embodiment, the polypeptides may be chemically synthesized.

The present invention further relates to the in vitro and in vivo production of GBV-B, mutated GBV-B or chimeric GBV-B/HCV viruses from the nucleic acid sequences of the invention.

In one embodiment, the sequences of the invention can be inserted into an expression vector that functions in eukaryotic cells. Eukaryotic expression vectors suitable for producing high efficiency gene transfer in vivo are well known to those of ordinary skill in the art and include, but are not limited to, plasmids, vaccinia viruses, retroviruses, adenoviruses and adeno-associated viruses.

In another embodiment, the sequences contained in the recombinant expression vector can be transcribed in vitro by methods known to those of ordinary skill in the art in order to produce RNA transcripts which encode the GBV-B of the invention. The GBV-B of the invention may then be produced by transfecting cells by methods known to those of ordinary skill in the art with either the in vitro transcription mixture containing the RNA

transcripts or with the recombinant expression vectors containing the nucleic acid sequences described herein.

In assaying the ability of the mutated GBV-B sequences or of the chimeric sequences of the invention to infect tamarins, the virulence phenotype of the virus produced by transfection of tamarins with the sequences of the invention can be monitored by methods known in the art such as measurement of liver enzyme levels (alanine aminotransferase (ALT) or isocitrate dehydrogenase (ICD)) or by histopathology of liver biopsies.

The present invention also relates to the use of the infectious GBV-B sequence, the mutated GBV-B nucleic acid sequences or the chimeric sequences of the invention to identify cell lines capable of supporting the replication of GBV-B or the chimeras of the invention.

Transfection of tissue culture cells with the nucleic acid sequences of the invention may be done by methods of transfection known in the art such as electroporation, precipitation with DEAE-Dextran or calcium phosphate, or incorporation into liposomes.

In one such embodiment, the method comprises the growing of animal cells <u>in vitro</u> and transfecting the cells with the nucleic acid of the invention, then determining if the cells show indicia of GBV-B or HCV infection. Such indicia include the detection of viral antigens in the cell, for example, by immunofluorescence procedures well known in the art; the detection of viral polypeptides by Western blotting using antibodies specific therefor; and the detection of newly transcribed viral RNA within the cells via methods such

as RT-PCR. The presence of live, infectious virus particles following such tests may also be shown by injection of cell culture medium or cell lysates into healthy, susceptible animals, with subsequent exhibition of the signs and symptoms of GBV-B infection.

Suitable cells or cell lines for culturing GBV-B or the chimeric GBV-B-HCV include, but are not limited to, lymphocyte and hepatocyte cell lines known in the art.

Alternatively, primary hepatocytes can be cultured, and then infected; or, the hepatocyte cultures could be derived from the livers of infected tamarins. In addition, various immortalization methods known to those of ordinary skill in the art can be used to obtain cell-lines derived from hepatocyte cultures. For example, primary hepatocyte cultures may be fused to a variety of cells to maintain stability.

The invention also provides that the nucleic acid sequences and viruses of the invention be supplied in the form of a kit, alone or in the form of a pharmaceutical composition.

All scientific publication and/or patents cited herein are specifically incorporated by reference. The following examples illustrate various aspects of the invention but are in no way intended to limit the scope thereof.

EXAMPLES

Materials and Methods

Source of GB virus B

Two tamarin pools VR-806, (American Type Culture Collection) and H205, were used for experimental

transmission of the GB virus agents to tamarins species *Saguinus mystax* and *Saguinus oedipus*.

Amplification, cloning and sequence analysis of GBV-B

Viral RNA was extracted from aliquots of the GB 2/94 serum pool or CT 11/91 liver homogenate with the TRIzol system (GIBCO/BRL). Primers used in cDNA synthesis and PCR amplification were based on the genomic sequence of GBV-B published by Simons et al (Simons 1995) shown in SEQ ID NO:3. Long RT-PCR was performed using Superscript II reverse transcriptase (GIBCO/BRL) and the Advantage cDNA polymerase mix (Clontech) as described previously (Tellier 1996). Four subgenomic regions of GBV-B covering the entire published sequence (Simons 1995) were amplified from serum and the PCR products were purified and cloned into pGEM-9Zf(-) (Promega) or pCR2.1 vector (Invitrogen) using standard procedures.

The 5' terminus of GBV-B was amplified from serum by using the rapid amplification of cDNA ends (RACE) with dC or dA tailing (GIBCO/BRL) and GBV-B specific antisense primers. Two different approaches were used to determine the 3' terminal sequence of GBV-B. In one approach, GBV-B RNA extracted from serum was circularized with T4 RNA ligase (Promega) and the 5'-to-3'-end-ligated viral RNA was amplified in RT-PCR using specific GBV-B primers. In the second approach, the 5' end of the negative strand GBV-B RNA extracted from the liver homogenate was amplified using the 5' RACE with dC tailing and GBV-B specific sense primers. The PCR products were cloned directly into pCR2.1-TOPO by using the TOPO TA Cloning Kit (Invitrogen).

The consensus sequence of GBV-B was determined by direct sequencing of PCR products (nucleotides 1-9078 and nucleotides 9130-9359) and by sequence analysis of the clones (nucleotides 1-7135 and nucleotides 7151-9399). Nucleotide positions correspond to those of the infectious clone (pGBB). Analyses of genomic sequences were performed with GeneWorks (Oxford Molecular Group) (Bukh 1995). To determine whether the GenBank data base contained sequences with homology to the GBV-B 3' UTR sequence identified in the present invention, a "Blast" search was performed. The predicted secondary structure of the GBV-B and HCV 3' UTR sequences were determined by the program "mfold" (Genetics Computer Group).

Construction of consensus cDNA clones of GBV-B

First, clone pGBB5-1, a consensus clone of GBV-B 2/94 containing the 3' terminus of GBV-B as published by Simons *et al* was constructed (Simons 1995a). The core sequence of the T7 promoter, a 5' guanosine residue and the sequence of GBV-B (9139 nucleotides) were cloned into pGEM-9Zf(-) vector using *Not*I/*Sac*I sites. A *BamH*I site was included at the GBV-B 3' terminus. Digested fragments containing the consensus sequence were purified from subclones and ligated using convenient sites. Next, a second consensus clone of GBV-B, clone pGBB, was constructed by inserting the additional 3' terminal sequence, amplified by PCR from one of the clones obtained by the RACE procedure described above, into pGBB5-1 using *Xma*I (at position 9114) and *BamH*I sites. A *Xho*I site was inserted following the GBV-B 3' terminus. DH5-alpha competent cells (GIBCO BRL) were transformed and selected on LB agar plates containing 100 μg/ml

ampicillin (SIGMA) and amplified in LB liquid cultures at 30°C for 18-20 hrs (Yanagi 1997). Each cDNA clone was re-transformed to select a single clone, and large-scale preparation of plasmid DNA was performed with a QIAGEN plasmid Maxi kit as described previously (Yanagi 1997). Each clone was genetically stable since the digestion pattern was as expected following retransformation and the complete sequence was the expected one.

Intrahepatic transfection of tamarins with transcribed GBV-B RNA

In 100 µl reactions, RNA was transcribed *in vitro* with T7 RNA polymerase (Promega) from 10 µg of linearized template plasmid. The plasmid pGBB5-1 was linearized with *BamHI* (Promega) and the plasmid pGBB was linearized with *Xho*I (Promega). The integrity of the RNA was checked by electrophoresis through agarose gel stained with ethidium bromide. Each transcription mixture was diluted with 400 µl of ice-cold phosphate-buffered saline without calcium or magnesium (SIGMA) and then immediately frozen on dry ice and stored at -80°C. Within 24 hours of synthesis, two transcription mixtures were injected into each tamarin by percutaneous intrahepatic injection guided by ultrasound (Emerson, 1992; Yanagi 1998, 1999). If the tamarin did not become infected, the same transfection was repeated once. All transfected animals were negative for GBV-A_{SM} as determined by the protocol described previously (Bukh 1997a).

Monitoring of experimental course in tamarins

Serum samples were collected weekly from the tamarins and monitored for liver enzyme levels [alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGT), and isocitrate dehydrogenase (ICD)] by standard methods and for GBV-B RNA by a specific reverse transcriptase-polymerase chain reaction (RT-PCR) assay. Total RNA was extracted from 100 µl of serum using the TRIzol reagent. The RNA pellet was resuspended in 10 mM dithiothreitol (DTT) containing 5% (vol/vol) of RNasin (20-40 u/µl) (Promega). The RT-nested PCR was performed with primers from the 5' UTR of GBV-B (external primer pair: 5'-CCT AGC AGG GCG TGG GGG ATT TCC-3' and 5'-AGG TCT GCG TCC TTG GTA GTG ACC-3'; internal primer pair: 5'-GGA TTT CCC CTG CCC GTC TG-3' and 5'-CCC CGG TCT TCC CTA CAG TG-3'). The reverse transcription was performed with avian myeloblastosis virus reverse transcriptase (Promega) and the external anti-sense primer and nested PCR was performed with AmpliTaq DNA polymerase or AmpliTaq Gold DNA polymerase (Perkin Elmer) as described previously (Bukh 1998a). Specificity was confirmed by sequence analysis of selected DNA products. Each set of experiments included a positive control sample (a 10^{-6} dilution of GB 8/93, estimated titer 100 genome equivalent (GE)) and appropriate negative control samples. The genome equivalent (GE) titer of GBV-B in positive samples was determined by RT-nested PCR on 10-fold serial dilutions of the extracted RNA (Bukh 1998a). One GE was defined as the number of GBV-B genomes present in the highest dilution positive in RT-nested PCR. The sensitivity of this RT-nested PCR assay for GBV-B was equivalent to that of our RT-nested PCR assay for HCV (Bukh 1998b), for example, conserved NS3

primers which had the same sensitivity for GBV-B as the 5' UTR primers could detect HCV at optimal sensitivity in samples with known HCV genome titer. Testing for GBV-A and GBV-A variants was performed by RT-nested PCR assays as described previously (Bukh 1997a).

The consensus sequence of the complete ORF was determined by direct sequencing of overlapping PCR products obtained by long RT-nested PCR on serum from one of the tamarins infected with RNA transcripts as previously described (Yanagi 1997).

Example 1

Transmission of GB Agent in Tamarins

To generate virus pools of the GB agent, tamarins were inoculated intravenously with pooled sera of the eleventh tamarin passage of this agent (Fig. 1). Acute phase sera from a *S. mystax* tamarin which developed hepatitis were pooled (GB 8/93) and inoculated into additional *S. mystax* tamarins to generate a second pool of acute phase serum (GB 2/94). Both serum pools contained approximately 10^8 GE/ml of GBV-B and GBV-A. A 10% liver homogenate (CT 11/91) was prepared from a *S. oedipus* tamarin which developed hepatitis following inoculation with the twelfth passage of the GB agent. The titer of GBV-B in the liver homogenate was approximately 10^7 GE/ml. The GB 2/94 serum and CT 11/91 liver samples were used as GBV-B cloning sources in the present study.

Inoculation of eight *S. mystax* tamarins with ten-fold serial dilutions of the GB 2/94 pool demonstrated that its infectivity titer of GBV-B was 10^8 tamarin 50% infectious doses (TID_{50}) (Fig. 2). The five

GBV-B infected tamarins all developed acute resolving hepatitis characterized by early appearance of viremia (weeks 1 or 2 p.i.), peak viral titers of 10^7-10^8 GE/ml and clearance of viremia after 9-16 weeks (Fig. 2). Two of these tamarins (*S. mystax* 769 and 777) were infected only with GBV-B and were negative for GBV-A and GBV-A_{SM}, whereas the other three tamarins were infected with both GBV-B and GBV-A_{SM}. A *S. mystax* tamarin inoculated with the liver homogenate also developed acute resolving hepatitis with peak GBV-B titers of 10^7 GE/ml and clearance of viremia after 11 weeks. Likewise, four *S. mystax* tamarins inoculated with dilutions of the GB 8/93 pool developed acute resolving hepatitis with clearance of the GBV-B virus after 11-26 weeks. Thus, GBV-B infection in *S. mystax* tamarins is characterized by acute hepatitis, early appearance of viremia, high peak viral titers and viral clearance.

Example 2

Novel 3' Terminal Sequence of GBV-B

The consensus sequence of the complete 5' UTR of GBV-B (nucleotides 1-445) was deduced from 13 clones containing nucleotides 1-283 and 3 clones containing nucleotides 31-445. In addition, the entire 5' UTR sequence was determined by direct sequencing of the amplicons. The sequences of the various clones were highly conserved and the consensus 5' UTR sequence of GBV-B from this pool was identical to that of the previously published sequence for GBV-B (Simons 1995a). It is noteworthy that 13 of 15 clones analyzed from the rapid amplification of cDNA ends (RACE) procedure contained the published GBV-B 5' terminus (A residue)

and that the same 5' terminus was obtained whether the 5' RACE was performed with dC or dA tailing.

The consensus sequence of the ORF (nucleotides 446-9037) was determined by direct sequencing of PCR products obtained using long RT-PCR (Yanagi 1997). In addition, 3 clones containing nts. 446-7135 (one of these clones had a deletion of nts. 3036-3636), 2 clones containing nts. 2019-3373, 5 clones containing nts. 7151-8261 and 7 clones containing nts. 7521-9037 were analyzed. The sequences of GBV-B clones in this pool were very homogeneous. Evidence of micro-heterogeneity was found at only 70 (0.8%) nucleotide and 36 (1.3%) amino acid positions, scattered throughout the ORF. The proportion of amino acid positions with heterogeneity ranged from 0.5-3.2% in different putative gene regions (lowest in NS3 and NS5B; highest in E2 and NS2). The GBV-B ORF sequence differed from the published sequence of GBV-B (Simons 1995) at 34 (0.4%) nucleotide and 12 (0.4%) deduced amino acid positions, respectively (Table 1).

Table 1

Nucleotide and amino acid differences among GBV-B (Simons 1995a), the consensus sequence of GBV-B recovered from a virus pool used as the cloning source (GBV-B, 2/94) and the infectious clone of GBV-B (pGBB).

Genomic Region*	Position nt [aa]	Nucleotide			Amino Acid		
		GBV-B	GBV-B 2/94	pGBB	GBV-B	GBV-B 2/94	PGBB
5' UTR (1-445)							
C (446-913)							
E1 (914-1489)	1030	C	T	T			
E2 (1490-2641)	1498	T	C (t)	C			
	1628 [395]	G	A (g)	A	V	I (V)	I
	2552 [703]	G	A (g)	A	D	N (D)	N
	2562,2563 [706]	C,A	A,C	A,C	P	H	H
	2566	T	T	T			
	2625 [727]	C	T	T	A	V	V
NS2 (2642-3385)	2647	C	T (c)	T			
	2816 [791]	C	T	T	L	F	F
	2855 [804]	A	G	G	T	A	A
	3235	A	G	G			
NS3 (3386-5125)	3475**	C	C (t)	T			
	3760	C	T (c)	T			
	4114	C	T	T			
	4117	C	A	A			
	4177	T	C	C			
	4615	C	T	T			
NS4A (5126-5290)							
NS4B (5291-6034)	5329	C	T	T			
	5332	T	C	C			
	5350	A	C	C			
	5455	C	T (c)	T			
NS5A (6035-7267)	6413 [1990]	T	A (t)	A	L	M (L)	M
	6577	G	T	T			
	6690 [2082]	T	C (t)	C	I	T(I)	T
	6965 [2174]	T	C (t)	C	S	P (S)	P
	7015	A	G (a)	G			
	7128 [2228]	G	A	A	G	E	E
	7138**	A	A	G			
	7142 [2233]	A	G	G	T	A	A
NS5B (7268-9037)	7282	T	C (t)	C			
	7849	C	A	A			
	7852	C	T	T			
	8942 [2981]	G	A (g)	A	V	I (V)	I
	8971	T	C	C			
	9026	C	T (c)	T			
3' UTR (9038-9399)	9067	T	C	C			
	Poly(U)	27 nts	11-23 nts	23 nts			
	9134	Deletion	C	C			
	9141-9399	ND	259 nts	259 nts			

*Nucleotide positions corresponding to pGBB. Putative gene borders defined as suggested by homology with HCV (Muerhoff 1995). No homology was observed at the NS2-NS3 junction.

**Positions that differ between the cloning source (GBV-B 2/94) and the infectious clone of GBV-B (pGBB). The change introduced into pGBB at position 7138 introduced an artificial *SalI* site. nd: Not determined. Nucleotides and amino acids shown in parenthesis were found as a minor species in the cloning source (GBV-B, 2/94

The sequence for the 3' UTR is shown in Figure 3. Additional 3' UTR sequence was initially identified by performing RT-PCR across 5'-to-3'-end-ligated viral RNA extracted from serum. In all 4 clones with GBV-B sequences, the 5' UTR was truncated compared to the published sequence (simon 1995a). However, whereas one clone (29c) had the exact 3' terminus previously published by Simons *et al*. (Simons 1995a), the three other clones (29a, 29b, 29d) had 150 additional terminal nucleotides. Compared with the published sequence, all four clones had a single nucleotide insertion (C residue) at position 9134. Next, RACE using dC-tailing only was performed on the 5' end of the negative-strand RNA extracted from the liver homogenate. All 11 clones analyzed had additional sequences at the 3' terminus. Compared with the published GBV-B sequence, two clones (gb6, gb23) had 259 additional nucleotides, 8 clones (gb9, gb19, gb20, gb21, gb24, gb25, gb30, gb35) had 236 additional nucleotides and 1 clone (gb8) had 232 additional nucleotides. Moreover, all of these clones had the insertion at position 9134. The 3' UTR sequences among the various clones were highly conserved (Fig. 3). To demonstrate that the terminal 22 nucleotides found only in clones gb6 and gb23 existed in circulating viruses, RT-nested PCR was performed on 10-fold serially diluted RNA extracted from the serum pool GB 2/94 using an RT and external antisense primer deduced from this sequence. GBV-B RNA was detected at a dilution of 10^{-7} and the sequence of the amplicon was identical to the sequence recovered from the liver homogenate. Thus, the 3' UTR of GBV-B consists of a short sequence of 30 nucleotides followed by a 11-24

nucleotide-long poly (U) tract (single C residues were observed in GBV-B from the liver homogenate) and a 3' terminal sequence of at least 309 nucleotides. The new GBV-B 3' UTR sequence did not have significant homology to any of the sequences deposited in the GenBank database. A prediction of the secondary structure of the 3' UTR sequence is shown in Figure 4. The most notable feature of the secondary structure is a highly stable stem-loop structure at the very 3' end consisting of 47 nucleotides.

Example 3

The pGBB Clone of GBV-B is Infectious *in vivo*

The infectivity of RNA transcripts from the consensus clone pGBB5-1 which encompassed only the published GBV-B sequence (Simons 1995) was first tested. Within the GBV-B sequence there were no deduced amino acid differences and only 2 nucleotide differences (at nucleotide positions 3475 and 7138) between the consensus sequence of the cloning source (GBV-B 2/94) and the sequence of pGBB5-1 clone. In addition, the 3' UTR of pGBB5-1 had a deletion at nucleotide position 9134 and was missing the 3' terminal 259 nucleotides (Fig. 3). Prior to transcription, the pGBB5-1 clone was linearized at the *BamHI* site with digestion at the exact GBV-B 3' terminus. The RNA transcripts from pGGB5-1 were injected into the liver of two tamarins (*S. mystax* 797 and 815). GBV-B RNA was not detected in weekly serum samples collected during 17 weeks of follow-up. As the susceptibility of these two tamarins to GBV-B was subsequently demonstrated by experimental infection using a GBV-B virus pool, the consensus clone pGBB5-1

which lacks the 3' terminal sequence of GBV-B is thus not infectious *in vivo*.

Next, the infectivity of RNA transcripts from the full-length consensus GBV-B cDNA clone pGBB was tested. The pGBB clone was identical to the pGBB5-1 clone except in the 3' UTR. Thus, in addition to a 5' UTR of 445 nucleotides, an ORF of 8592 nucleotides encoding 2864 amino acids and a 3' UTR of 103 nucleotides, the pGBB clone also contains an additional 259 nucleotides in its 3′ UTR. pGBB was linearized at the *Xho*I site which added an additional C residue at the 3' end of the transcribed GBV-B RNA. When RNA transcripts from the pGBB clone were injected into the liver of two tamarins (*S. mystax* 816 and 817), both tamarins became infected with GBV-B with viremia at week 1 p.i. and peak viral titers of 10^8 GE/ml (Fig. 5). The consensus sequence of PCR products of the complete ORF, amplified from serum obtained during week 2 p.i. from one tamarin (*S. mystax* 817), was identical to the sequence of pGBB, including at the two positions which differed from the consensus sequence of the cloning source and from the published sequence of GBV-B (Table 1). By performing RT-PCR as desired above, it was demonstrated that the very 3' terminal GBV-B sequence of pGBB existed in the circulating viruses in this tamarin. Within two weeks of the transfection both tamarins developed hepatitis with dramatically elevated liver enzyme levels (Fig. 5). Thus, the pGBB clone is infectious *in vivo* whereas the clone pGBB5-1 which lacks the last 259 nucleotides was not.

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WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule which encodes GB virus-B, said molecule capable of expressing said virus when transfected into cells.

2. The nucleic acid molecule of claim 1, wherein said molecule encodes the amino acid sequence of SEQ ID NO:2.

3. The nucleic acid molecule of claim 2, wherein said molecule comprises the nucleic acid sequence of SEQ ID NO:1.

4. A DNA construct comprising a nucleic acid molecule according to claim 1.

5. A DNA construct comprising a nucleic acid molecule according to claim 3.

6. An RNA transcript of the DNA construct of claims 4 or 5.

7. A cell transfected with the DNA construct of claims 4 or 5.

8. A cell transfected with RNA transcripts of claim 6.

9. A GB virus-B polypeptide produced by the cell of claim 7.

10. A GB virus-B polypeptide produced by the cell of claim 8.

11. A GB virus-B produced by the cell of claim 7.

12. A GB virus-B produced by the cell of claim 8.

13. A GB virus-B whose genome comprises a nucleic acid molecule according to claim 1.

14. A GB virus-B whose genome comprises a nucleic acid molecule according to claim 3.

15. A method for producing a GB virus-B comprising transfecting a host cell with the DNA construct of claims 4 or 5.

16. A method for producing a GB virus-B comprising transfecting a host cell with the RNA transcript of claim 6.

17. A composition comprising a nucleic acid molecule of claim 1 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

18. A composition comprising a nucleic acid molecule of claim 3 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

19. A nucleic acid molecule comprising a chimeric virus genome, said genome being a GB virus-B genome according to claim 1 in which a 3′ or 5′ UTR sequence of the genome is replaced by a corresponding region of the 3′ or 5′ UTR sequence of a hepatitis C virus genome.

20. The nucleic acid molecule of claim 19, wherein a 3′ UTR sequence of the genome of a GB virus-B is replaced by a corresponding 3′ UTR sequence of a hepatitis C virus genome.

21. The nucleic acid molecule of claim 20, wherein the 3′ UTR sequence is the 3′ UTR terminal stem loop sequence.

22. The nucleic acid molecule of claim 19, wherein a 5′ UTR sequence of the genome of a GB virus-B has been replaced by a corresponding 5′ UTR sequence of a hepatitis C virus genome.

23. The nucleic acid molecule of claim 22, wherein the 5′ UTR sequence is the IRES sequence.

24. A nucleic acid molecule comprising a chimeric virus genome, said genome being a GB virus-B genome according to claim 1 in which the non-structural region of the genome of a GB virus-B has been replaced by the non-structural region of a hepatitis C virus genome.

25. The nucleic acid molecule of claim 24, wherein at least one gene from the non-structural region of the genome of a GB virus-B has been replaced by the corresponding gene from the non-structural region of a hepatitis C virus genome.

26. The nucleic acid molecule of claim 25, wherein the gene from the non-structural region is selected from the group consisting of NS3 protease, NS3 RNA helicase, or NS5B RNA polymerase.

27. A nucleic acid molecule comprising a chimeric virus genome, said genome being a GB virus-B genome according to claim 1 in which the structural region of the genome of a GB virus-B has been replaced by the structural region of a hepatitis C virus genome.

28. The nucleic acid molecule of claim 27, wherein at least one gene from the structural region of the genome of a GB virus-B has been replaced by the

corresponding gene from the structural region of a hepatitis C virus genome.

29. The nucleic acid molecule of claim 28, wherein the gene from the structural region is selected from the group consisting of E1, E2 or C.

30. The nucleic acid molecule of claim 28, wherein the E1 and E2 genes from the structural region of the genome of a GB virus-B have been replaced by the E1 and E2 genes of a hepatitis C virus genome.

31. The nucleic acid molecule of claim 28, wherein the E1 gene from the structural region of the genome of a GB virus-B has been replaced by the E1 gene of a hepatitis C virus genome.

32. The nucleic acid molecule of claim 28, wherein the E2 gene from the structural regions of the genome of a GB virus-B has been replaced by the E2 gene of a hepatitis C virus genome.

33. A DNA construct comprising the nucleic acid molecule of claims 19, 24 or 27.

34. An RNA transcript of the DNA construct of claim 33.

35. A virus whose genome comprises a nucleic acid molecule according to claims 19, 24 or 27.

36. A nucleic acid molecule comprising a chimeric virus genome, said genome being a hepatitis C virus genome in which a 3′ or 5′ UTR sequence of the genome is replaced by a corresponding region of the 3′ or 5′ UTR sequence of a GB virus-B genome according to claim 1.

37. A nucleic acid molecule comprising a chimeric virus genome, said genome being a hepatitis C virus genome in which the non-structural region of the genome has been replaced by the non-structural region of a GB virus-B genome according to claim 1.

38. A nucleic acid molecule comprising a chimeric virus genome, said genome being a hepatitis C virus genome in which the structural region of the genome has been replaced by the structural region of a GB virus-B genome according to claim 1.

39. A polypeptide encoded by the nucleic acid molecule of claims 19, 24 or 27.

40. A polypeptide encoded by the nucleic acid molecule of claims 36, 37 or 38.

FIG. 1

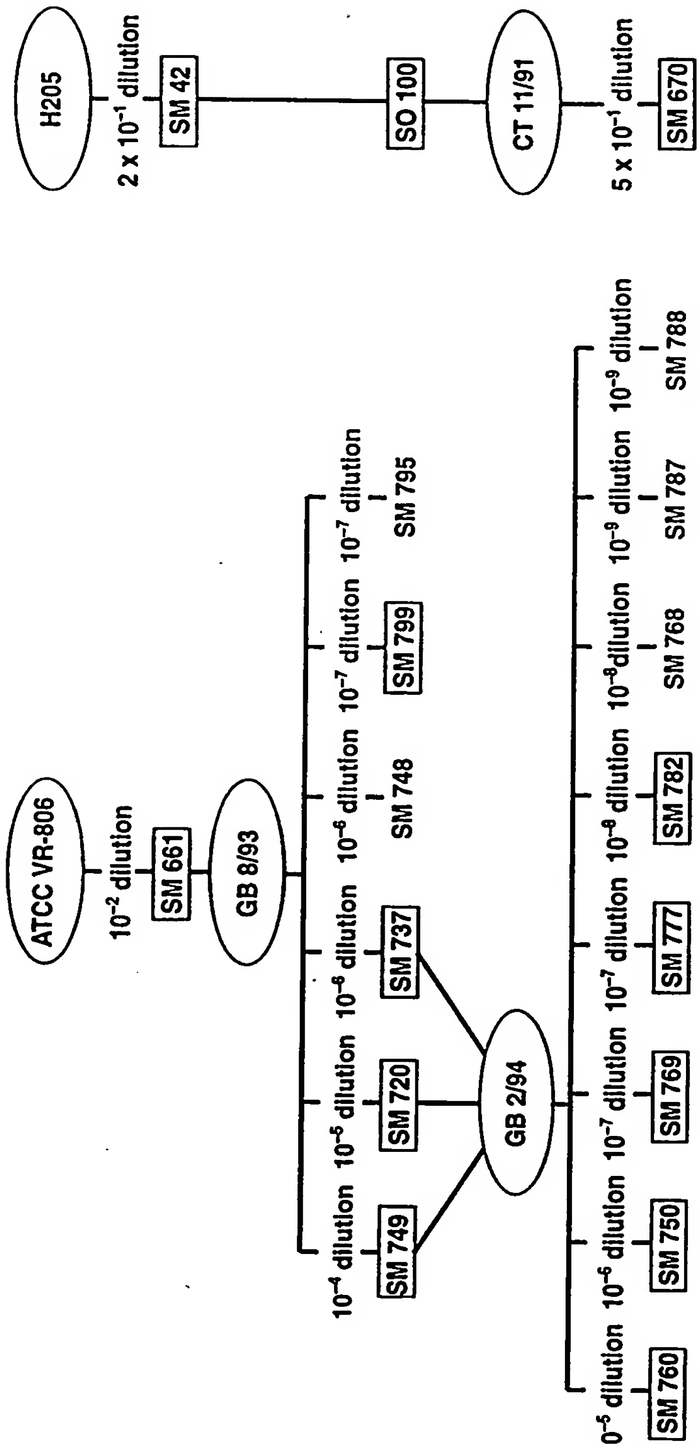
ATCC VR-806
10^{-2} dilution
SM 661
GB 8/93
10^{-4} dilution
SM 749
10^{-5} dilution
SM 720
10^{-6} dilution
SM 737
10^{-6} dilution
SM 748
10^{-7} dilution
SM 799
10^{-7} dilution
SM 795
GB 2/94
10^{-5} dilution
SM 760
10^{-6} dilution
SM 750
10^{-7} dilution
SM 769
10^{-7} dilution
SM 777
10^{-8} dilution
SM 782
10^{-8}dilution
SM 768
10^{-9} dilution
SM 787
10^{-9} dilution
SM 788
H205
2×10^{-1} dilution
SM 42
SO 100
CT 11/91
5×10^{-1} dilution
SM 670

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FIG. 2

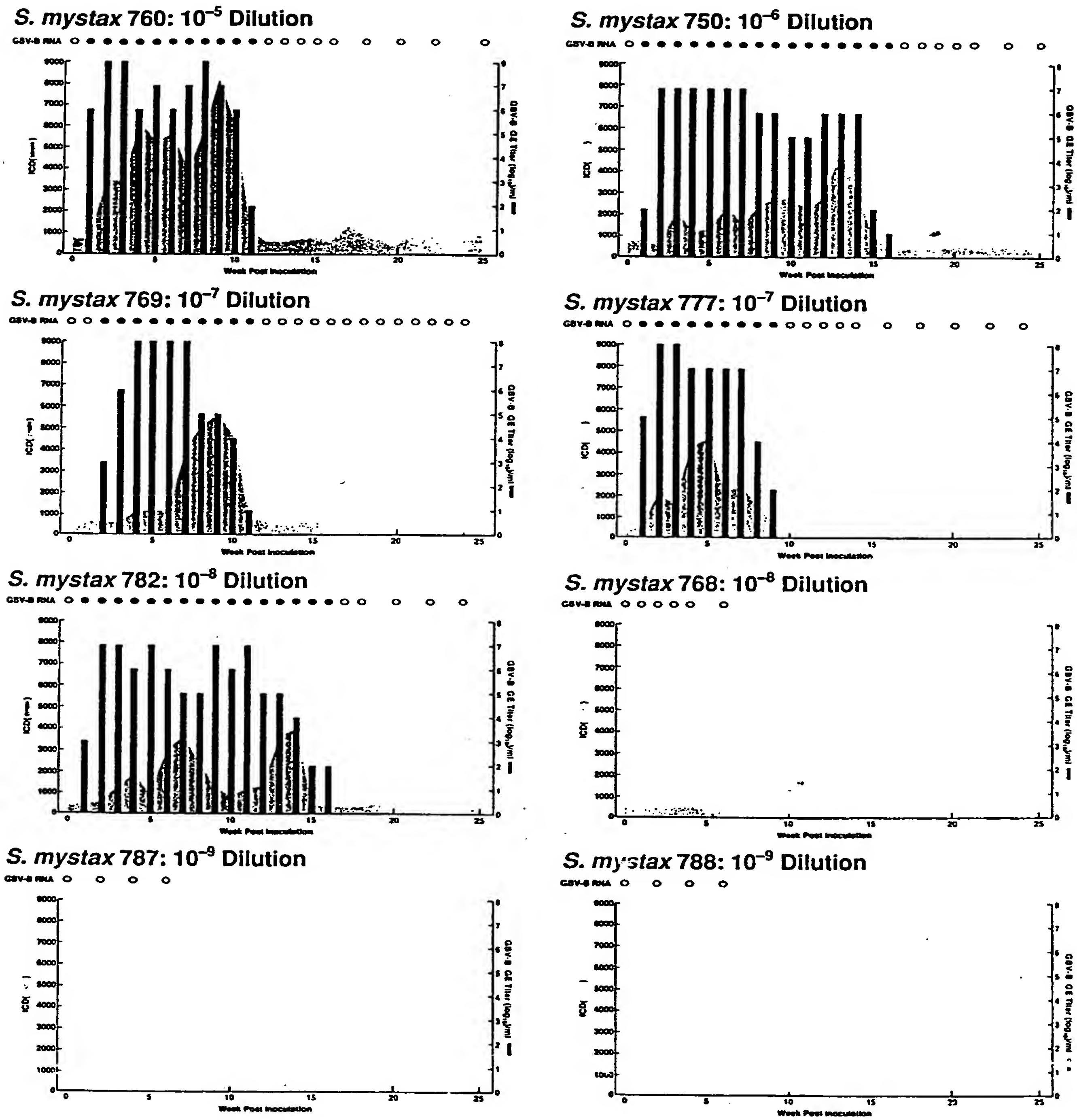

S. mystax 760: 10^{-5} Dilution
S. mystax 750: 10^{-6} Dilution
S. mystax 769: 10^{-7} Dilution
S. mystax 777: 10^{-7} Dilution
S. mystax 782: 10^{-8} Dilution
S. mystax 768: 10^{-8} Dilution
S. mystax 787: 10^{-9} Dilution
S. mystax 788: 10^{-9} Dilution

FIG. 3

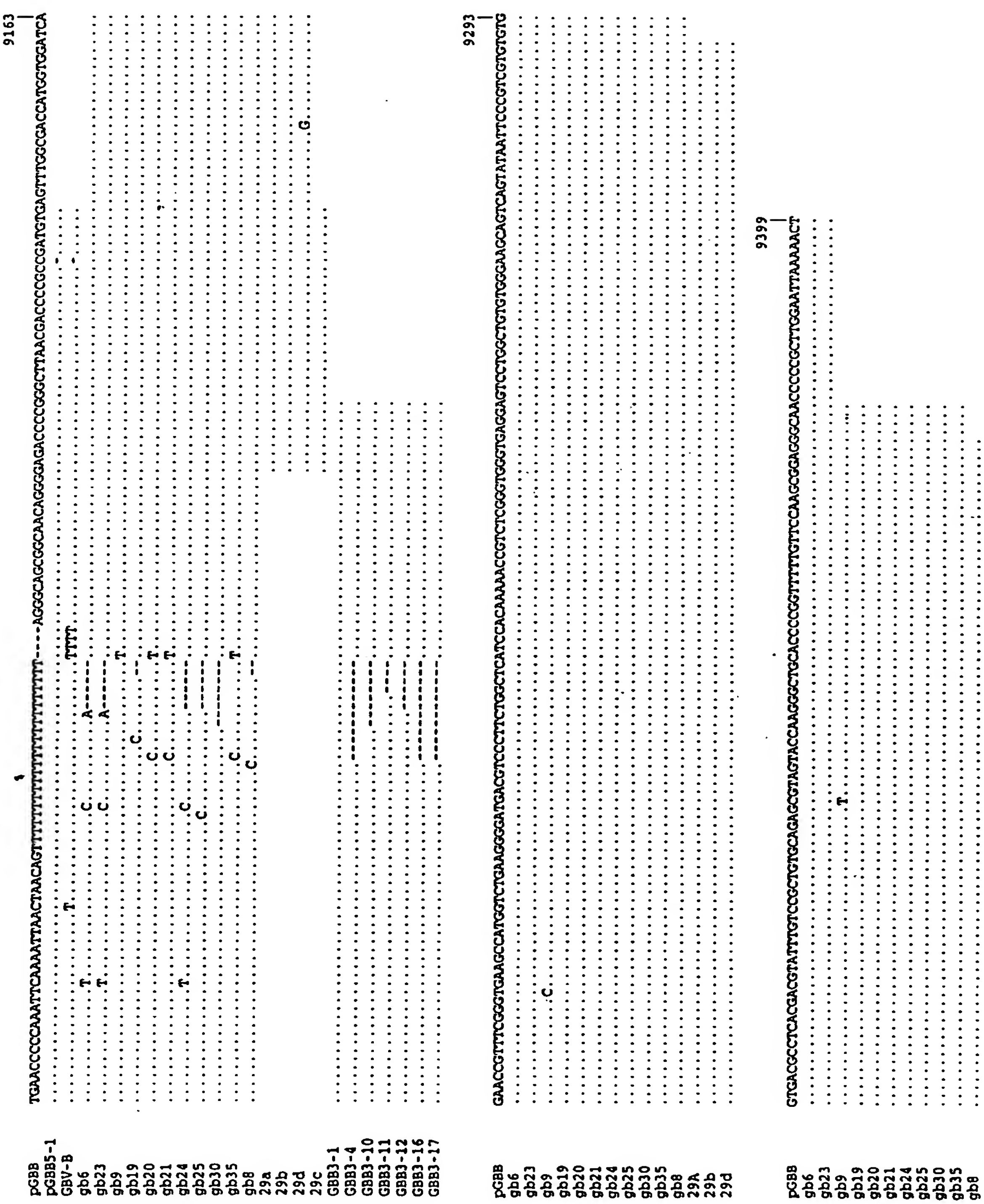
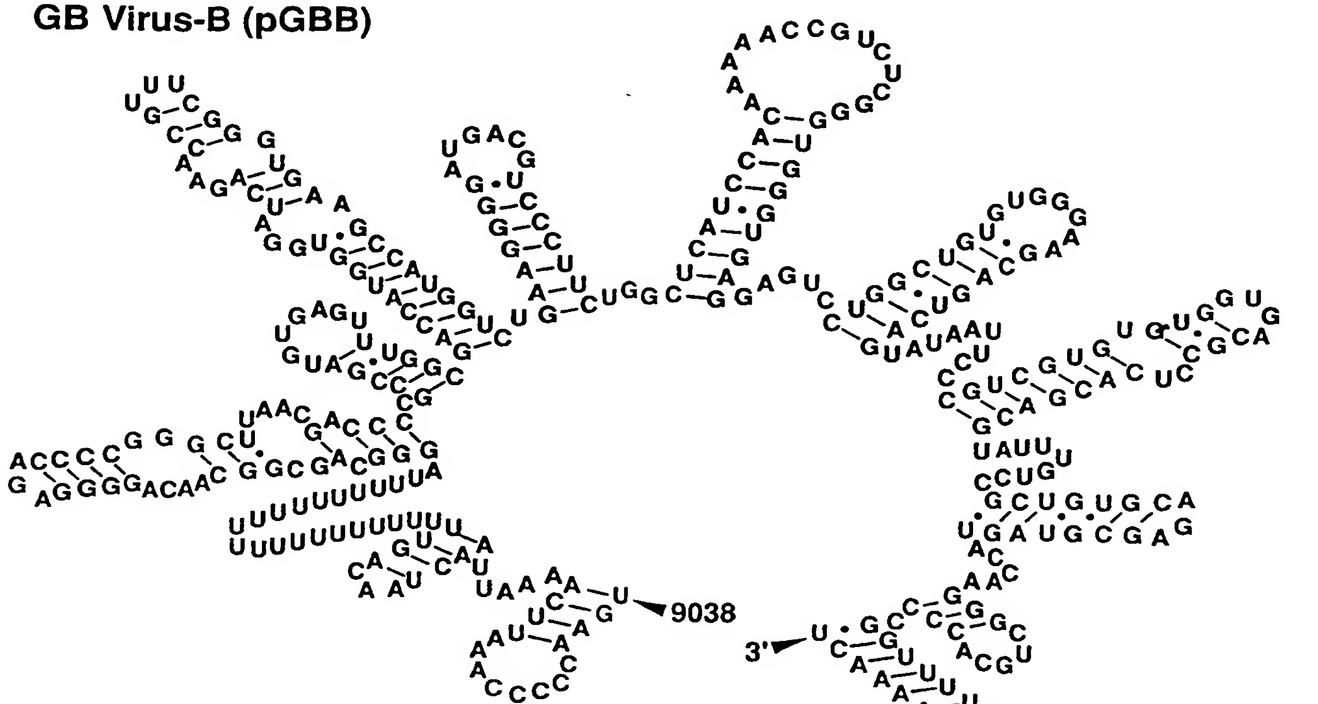

pGBB
pGBB5-1
GBV-B
gb6
gb23
gb9
gb19
gb20
gb21
gb24
gb25
gb30
gb35
gb8
29a
29b
29d
29c
GBB3-1
GBB3-4
GBB3-10
GBB3-11
GBB3-12
GBB3-16
GBB3-17
9163
9293
9399

FIG. 4

GB Virus-B (pGBB)



Hepatitis C Virus (pCV-H77C)

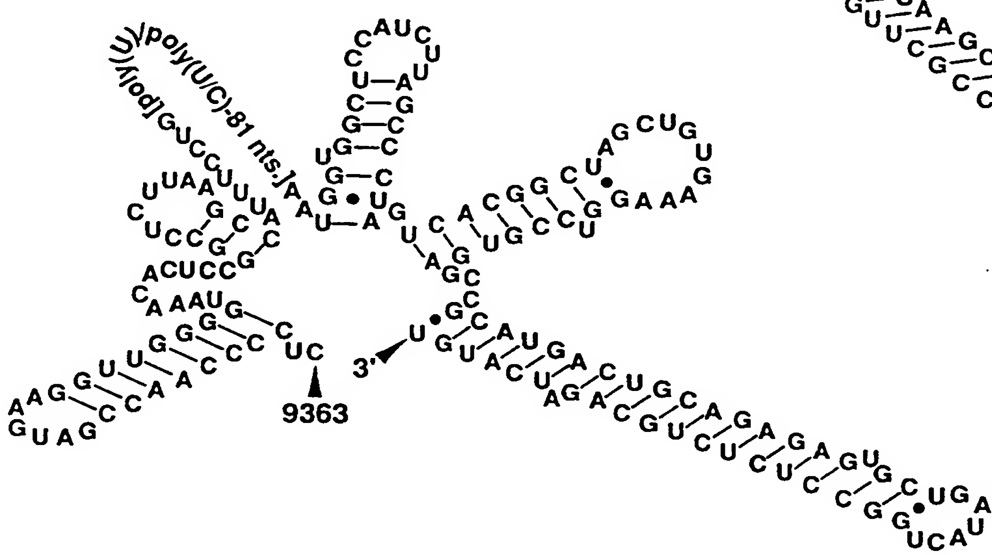
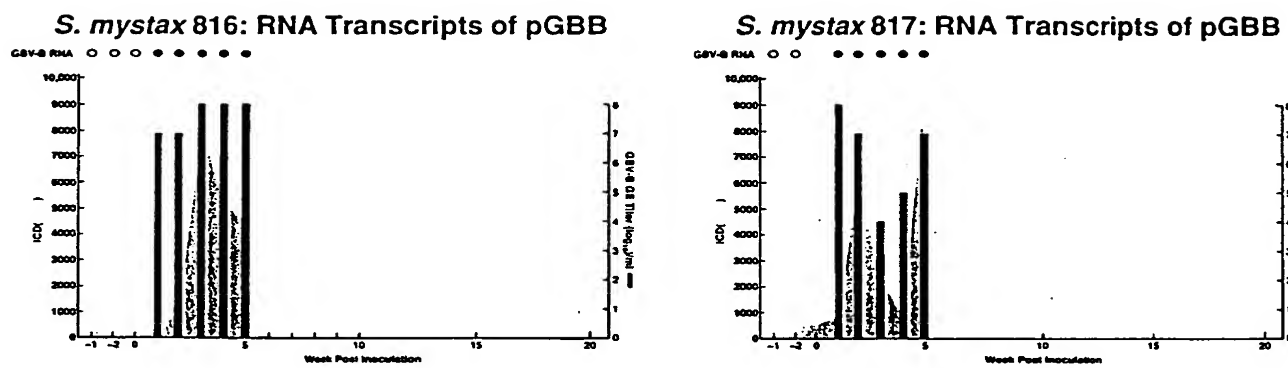


FIG. 5


S. mystax 816: RNA Transcripts of pGBB
S. mystax 817: RNA Transcripts of pGBB
Week Post Inoculation

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GCCAGCCCCC	TGATGGGGGC	GACACTCCAC	CATGAATCAC	TCCCCTGTGA	50
GGAACTACTG	TCTTCACGCA	GAAAGCGTCT	AGCCATGGCG	TTAGTATGAG	100
TGTCGTGCAG	CCTCCAGGAC	CCCCCCTCCC	GGGAGAGCCA	TAGTGGTCTG	150
CGGAACCGGT	GAGTACACCG	GAATTGCCAG	GACGACCGGG	TCCTTTCTTG	200
GATAAACCCG	CTCAATGCCT	GGAGATTTGG	GCGTGCCCCC	GCAAGACTGC	250
TAGCCGAGTA	GTGTTGGGTC	GCGAAAGGCC	TTGTGGTACT	GCCTGATAGG	300
GTGCTTGCGA	GTGCCCCGGG	AGGTCTCGTA	GACCGTGCAC	CATGAGCACG	350
AATCCTAAAC	CTCAAAGAAA	AACCAAACGT	AACACCAACC	GTCGCCCACA	400
GGACGTCAAG	TTCCCGGGTG	GCGGTCAGAT	CGTTGGTGGA	GTTTACTTGT	450
TGCCGCGCAG	GGGCCCTAGA	TTGGGTGTGC	GCGCGACGAG	GAAGACTTCC	500
GAGCGGTCGC	AACCTCGAGG	TAGACGTCAG	CCTATCCCCA	AGGCACGTCG	550
GCCCGAGGGC	AGGACCTGGG	CTCAGCCCGG	GTACCCTTGG	CCCCTCTATG	600
GCAATGAGGG	TTGCGGGTGG	GCGGGATGGC	TCCTGTCTCC	CCGTGGCTCT	650
CGGCCTAGCT	GGGGCCCCAC	AGACCCCCGG	CGTAGGTCGC	GCAATTTGGG	700
TAAGGTCATC	GATACCCTTA	CGTGCGGCTT	CGCCGACCTC	ATGGGGTACA	750
TACCGCTCGT	CGGCGCCCCT	CTTGGAGGCG	CTGCCAGGGC	CCTGGCGCAT	800
GGCGTCCGGG	TTCTGGAAGA	CGGCGTGAAC	TATGCAACAG	GGAACCTTCC	850
TGGTTGCTCT	TTCTCTATCT	TCCTTCTGGC	CCTGCTCTCT	TGCCTGACTG	900
TGCCCGCTTC	AGCCTACCAA	GTGCGCAATT	CCTCGGGGCT	TTACCATGTC	950
ACCAATGATT	GCCCTAACTC	GAGTATTGTG	TACGAGGCGG	CCGATGCCAT	1000
CCTGCACACT	CCGGGGTGTG	TCCCTTGCGT	TCGCGAGGGT	AACGCCTCGA	1050
GGTGTTGGGT	GGCGGTGACC	CCCACGGTGG	CCACCAGGGA	CGGCAAACTC	1100
CCCACAACGC	AGCTTCGACG	TCATATCGAT	CTGCTTGTCG	GGAGCGCCAC	1150
CCTCTGCTCG	GCCCTCTACG	TGGGGGACCT	GTGCGGGTCT	GTCTTTCTTG	1200
TTGGTCAACT	GTTTACCTTC	TCTCCCAGGC	GCCACTGGAC	GACGCAAGAC	1250
TGCAATTGTT	CTATCTATCC	CGGCCATATA	ACGGGTCATC	GCATGGCATG	1300
GGATATGATG	ATGAACTGGT	CCCCTACGGC	AGCGTTGGTG	GTAGCTCAGC	1350
TGCTCCGGAT	CCCACAAGCC	ATCATGGACA	TGATCGCTGG	TGCTCACTGG	1400
GGAGTCCTGG	CGGGCATAGC	GTATTTCTCC	ATGGTGGGGA	ACTGGGCGAA	1450
GGTCCTGGTA	GTGCTGCTGC	TATTTGCCGG	CGTCGACGCG	GAAACCCACG	1500
TCACCGGGGG	AAATGCCGGC	CGCACCACGG	CTGGGCTTGT	TGGTCTCCTT	1550
ACACCAGGCG	CCAAGCAGAA	CATCCAACTG	ATCAACACCA	ACGGCAGTTG	1600
GCACATCAAT	AGCACGGCCT	TGAATTGCAA	TGAAAGCCTT	AACACCGGCT	1650
GGTTAGCAGG	GCTCTTCTAT	CAACACAAAT	TCAACTCTTC	AGGCTGTCCT	1700
GAGAGGTTGG	CCAGCTGCCG	ACGCCTTACC	GATTTTGCCC	AGGGCTGGGG	1750
TCCTATCAGT	TATGCCAACG	GAAGCGGCCT	CGACGAACGC	CCCTACTGCT	1800
GGCACTACCC	TCCAAGACCT	TGTGGCATTG	TGCCCGCAAA	GAGCGTGTGT	1850
GGCCCGGTAT	ATTGCTTCAC	TCCCAGCCCC	GTGGTGGTGG	GAACGACCGA	1900

FIG. 6A

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
CAGGTCGGGC	GCGCCTACCT	ACAGCTGGGG	TGCAAATGAT	ACGGATGTCT	1950
TCGTCCTTAA	CAACACCAGG	CCACCGCTGG	GCAATTGGTT	CGGTTGTACC	2000
TGGATGAACT	CAACTGGATT	CACCAAAGTG	TGCGGAGCGC	CCCCTTGTGT	2050
CATCGGAGGG	GTGGGCAACA	ACACCTTGCT	CTGCCCCACT	GATTGCTTCC	2100
GCAAACATCC	GGAAGCCACA	TACTCTCGGT	GCGGCTCCGG	TCCCTGGATT	2150
ACACCCAGGT	GCATGGTCGA	CTACCCGTAT	AGGCTTTGGC	ACTATCCTTG	2200
TACCATCAAT	TACACCATAT	TCAAAGTCAG	GATGTACGTG	GGAGGGGTCG	2250
AGCACAGGCT	GGAAGCGGCC	TGCAACTGGA	CGCGGGGCGA	ACGCTGTGAT	2300
CTGGAAGACA	GGGACAGGTC	CGAGCTCAGC	CCGTTGCTGC	TGTCCACCAC	2350
ACAGTGGCAG	GTCCTTCCGT	GTTCTTTCAC	GACCCTGCCA	GCCTTGTCCA	2400
CCGGCCTCAT	CCACCTCCAC	CAGAACATTG	TGGACGTGCA	GTACTTGTAC	2450
GGGGTAGGGT	CAAGCATCGC	GTCCTGGGCC	ATTAAGTGGG	AGTACGTCGT	2500
TCTCCTGTTC	CTTCTGCTTG	CAGACGCGCG	CGTCTGCTCC	TGCTTGTGGA	2550
TGATGTTACT	CATATCCCAA	GCGGAGGCGG	CTTTGGAGAA	CCTCGTAATA	2600
CTCAATGCAG	CATCCCTGGC	CGGGACGCAC	GGTCTTGTGT	CCTTCCTCGT	2650
GTTCTTCTGC	TTTGCGTGGT	ATCTGAAGGG	TAGGTGGGTG	CCCGGAGCGG	2700
TCTACGCCCT	CTACGGGATG	TGGCCTCTCC	TCCTGCTCCT	GCTGGCGTTG	2750
CCTCAGCGGG	CATACGCACT	GGACACGGAG	GTGGCCGCGT	CGTGTGGCGG	2800
CGTTGTTCTT	GTCGGGTTAA	TGGCGCTGAC	TCTGTCGCCA	TATTACAAGC	2850
GCTATATCAG	CTGGTGCATG	TGGTGGCTTC	AGTATTTTCT	GACCAGAGTA	2900
GAAGCGCAAC	TGCACGTGTG	GGTTCCCCCC	CTCAACGTCC	GGGGGGGCGG	2950
CGATGCCGTC	ATCTTACTCA	TGTGTGTAGT	ACACCCGACC	CTGGTATTTG	3000
ACATCACCAA	ACTACTCCTG	GCCATCTTCG	GACCCCTTTG	GATTCTTCAA	3050
GCCAGTTTGC	TTAAAGTCCC	CTACTTCGTG	CGCGTTCAAG	GCCTTCTCCG	3100
GATCTGCGCG	CTAGCGCGGA	AGATAGCCGG	AGGTCATTAC	GTGCAAATGG	3150
CCATCATCAA	GTTAGGGGCG	CTTACTGGCA	CCTATGTGTA	TAACCATCTC	3200
ACCCCTCTTC	GAGACTGGGC	GCACAACGGC	CTGCGAGATC	TGGCCGTGGC	3250
TGTGGAACCA	GTCGTCTTCT	CCCGAATGGA	GACCAAGCTC	ATCACGTGGG	3300
GGGCAGATAC	CGCCGCGTGC	GGTGACATCA	TCAACGGCTT	GCCCGTCTCT	3350
GCCCGTAGGG	GCCAGGAGAT	ACTGCTTGGG	CCAGCCGACG	GAATGGTCTC	3400
CAAGGGGTGG	AGGTTGCTGG	CGCCCATCAC	GGCGTACGCC	CAGCAGACGA	3450
GAGGCCTCCT	AGGGTGTATA	ATCACCAGCC	TGACTGGCCG	GGACAAAAAC	3500
CAAGTGGAGG	GTGAGGTCCA	GATCGTGTCA	ACTGCTACCC	AAACCTTCCT	3550
GGCAACGTGC	ATCAATGGGG	TATGCTGGAC	TGTGTACCAC	GGGGCCGGAA	3600
CGAGGACCAT	CGCATCACCC	AAGGGTCCTG	TCATCCAGAT	GTATACCAAT	3650
GTGGACCAAG	ACCTTGTGGG	CTGGCCCGCT	CCTCAAGGTT	CCCGCTCATT	3700
GACACCCTGT	ACCTGCGGCT	CCTCGGACCT	TTACCTGGTC	ACGAGGCACG	3750
CCGATGTCAT	TCCCGTGCGC	CGGCGAGGTG	ATAGCAGGGG	TAGCCTGCTT	3800

FIG. 6B

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H77C

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TCGCCCCGGC CCATTTCCTA CTTGAAAGGC TCCTCGGGGG GTCCGCTGTT   3850
GTGCCCCGCG GGACACGCCG TGGGCCTATT CAGGGCCGCG GTGTGCACCC   3900
GTGGAGTGGC TAAAGCGGTG GACTTTATCC CTGTGGAGAA CCTAGGGACA   3950
ACCATGAGAT CCCCGGTGTT CACGGACAAC TCCTCTCCAC CAGCAGTGCC   4000
CCAGAGCTTC CAGGTGGCCC ACCTGCATGC TCCCACCGGC AGCGGTAAGA   4050
GCACCAAGGT CCCGGCTGCG TACGCAGCCC AGGGCTACAA GGTGTTGGTG   4100
CTCAACCCCT CTGTTGCTGC AACGCTGGGC TTTGGTGCTT ACATGTCCAA   4150
GGCCCATGGG GTTGATCCTA ATATCAGGAC CGGGGTGAGA ACAATTACCA   4200
CTGGCAGCCC CATCACGTAC TCCACCTACG GCAAGTTCCT TGCCGACGGC   4250
GGGTGCTCAG GAGGTGCTTA TGACATAATA ATTTGTGACG AGTGCCACTC   4300
CACGGATGCC ACATCCATCT TGGGCATCGG CACTGTCCTT GACCAAGCAG   4350
AGACTGCGGG GGCGAGACTG GTTGTGCTCG CCACTGCTAC CCCTCCGGGC   4400
TCCGTCACTG TGTCCCATCC TAACATCGAG GAGGTTGCTC TGTCCACCAC   4450
CGGAGAGATC CCCTTTTACG GCAAGGCTAT CCCCCTCGAG GTGATCAAGG   4500
GGGGAAGACA TCTCATCTTC TGCCACTCAA AGAAGAAGTG CGACGAGCTC   4550
GCCGCGAAGC TGGTCGCATT GGGCATCAAT GCCGTGGCCT ACTACCGCGG   4600
TCTTGACGTG TCTGTCATCC CGACCAGCGG CGATGTTGTC GTCGTGTCGA   4650
CCGATGCTCT CATGACTGGC TTTACCGGCG ACTTCGACTC TGTGATAGAC   4700
TGCAACACGT GTGTCACTCA GACAGTCGAT TTCAGCCTTG ACCCTACCTT   4750
TACCATTGAG ACAACCACGC TCCCCCAGGA TGCTGTCTCC AGGACTCAAC   4800
GCCGGGGCAG GACTGGCAGG GGGAAGCCAG GCATCTATAG ATTTGTGGCA   4850
CCGGGGGAGC GCCCCTCCGG CATGTTCGAC TCGTCCGTCC TCTGTGAGTG   4900
CTATGACGCG GGCTGTGCTT GGTATGAGCT CACGCCCGCC GAGACTACAG   4950
TTAGGCTACG AGCGTACATG AACACCCCGG GGCTTCCCGT GTGCCAGGAC   5000
CATCTTGAAT TTTGGGAGGG CGTCTTTACG GGCCTCACTC ATATAGATGC   5050
CCACTTTTTA TCCCAGACAA AGCAGAGTGG GGAGAACTTT CCTTACCTGG   5100
TAGCGTACCA AGCCACCGTG TGCGCTAGGG CTCAAGCCCC TCCCCCATCG   5150
TGGGACCAGA TGTGGAAGTG TTTGATCCGC CTTAAACCCA CCCTCCATGG   5200
GCCAACACCC CTGCTATACA GACTGGGCGC TGTTCAGAAT GAAGTCACCC   5250
TGACGCACCC AATCACCAAA TACATCATGA CATGCATGTC GGCCGACCTG   5300
GAGGTCGTCA CGAGCACCTG GGTGCTCGTT GGCGGCGTCC TGGCTGCTCT   5350
GGCCGCGTAT TGCCTGTCAA CAGGCTGCGT GGTCATAGTG GGCAGGATCG   5400
TCTTGTCCGG GAAGCCGGCA ATTATACCTG ACAGGGAGGT TCTCTACCAG   5450
GAGTTCGATG AGATGGAAGA GTGCTCTCAG CACTTACCGT ACATCGAGCA   5500
AGGGATGATG CTCGCTGAGC AGTTCAAGCA GAAGGCCCTC GGCCTCCTGC   5550
AGACCGCGTC CCGCCATGCA GAGGTTATCA CCCCTGCTGT CCAGACCAAC   5600
TGGCAGAAAC TCGAGGTCTT TTGGGCGAAG CACATGTGGA ATTTCATCAG   5650
TGGGATACAA TACTTGGCGG GCCTGTCAAC GCTGCCTGGT AACCCCGCCA   5700
```

FIG. 6C

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TTGCTTCATT	GATGGCTTTT	ACAGCTGCCG	TCACCAGCCC	ACTAACCACT	5750
GGCCAAACCC	TCCTCTTCAA	CATATTGGGG	GGGTGGGTGG	CTGCCCAGCT	5800
CGCCGCCCCC	GGTGCCGCTA	CTGCCTTTGT	GGGTGCTGGC	CTAGCTGGCG	5850
CCGCCATCGG	CAGCGTTGGA	CTGGGGAAGG	TCCTCGTGGA	CATTCTTGCA	5900
GGGTATGGCG	CGGGCGTGGC	GGGAGCTCTT	GTAGCATTCA	AGATCATGAG	5950
CGGTGAGGTC	CCCTCCACGG	AGGACCTGGT	CAATCTGCTG	CCCGCCATCC	6000
TCTCGCCTGG	AGCCCTTGTA	GTCGGTGTGG	TCTGCGCAGC	AATACTGCGC	6050
CGGCACGTTG	GCCCGGGCGA	GGGGGCAGTG	CAATGGATGA	ACCGGCTAAT	6100
AGCCTTCGCC	TCCCGGGGGA	ACCATGTTTC	CCCCACGCAC	TACGTGCCGG	6150
AGAGCGATGC	AGCCGCCCGC	GTCACTGCCA	TACTCAGCAG	CCTCACTGTA	6200
ACCCAGCTCC	TGAGGCGACT	GCATCAGTGG	ATAAGCTCGG	AGTGTACCAC	6250
TCCATGCTCC	GGTTCCTGGC	TAAGGGACAT	CTGGGACTGG	ATATGCGAGG	6300
TGCTGAGCGA	CTTTAAGACC	TGGCTGAAAG	CCAAGCTCAT	GCCACAACTG	6350
CCTGGGATTC	CCTTTGTGTC	CTGCCAGCGC	GGGTATAGGG	GGGTCTGGCG	6400
AGGAGACGGC	ATTATGCACA	CTCGCTGCCA	CTGTGGAGCT	GAGATCACTG	6900
GACATGTCAA	AAACGGGACG	ATGAGGATCG	TCGGTCCTAG	GACCTGCAGG	6950
AACATGTGGA	GTGGGACGTT	CCCCATTAAC	GCCTACACCA	CGGGCCCCTG	6550
TACTCCCCTT	CCTGCGCCGA	ACTATAAGTT	CGCGCTGTGG	AGGGTGTCTG	6600
CAGAGGAATA	CGTGGAGATA	AGGCGGGTGG	GGGACTTCCA	CTACGTATCG	6650
GGTATGACTA	CTGACAATCT	TAAATGCCCG	TGCCAGATCC	CATCGCCCGA	6700
ATTTTTCACA	GAATTGGACG	GGGTGCGCCT	ACACAGGTTT	GCGCCCCCTT	6750
GCAAGCCCTT	GCTGCGGGAG	GAGGTATCAT	TCAGAGTAGG	ACTCCACGAG	6800
TACCCGGTGG	GGTCGCAATT	ACCTTGCGAG	CCCGAACCGG	ACGTAGCCGT	6850
GTTGACGTCC	ATGCTCACTG	ATCCCTCCCA	TATAACAGCA	GAGGCGGCCG	6900
GGAGAAGGTT	GGCGAGAGGG	TCACCCCCTT	CTATGGCCAG	CTCCTCGGCT	6950
AGCCAGCTGT	CCGCTCCATC	TCTCAAGGCA	ACTTGCACCG	CCAACCATGA	7000
CTCCCCTGAC	GCCGAGCTCA	TAGAGGCTAA	CCTCCTGTGG	AGGCAGGAGA	7050
TGGGCGGCAA	CATCACCAGG	GTTGAGTCAG	AGAACAAAGT	GGTGATTCTG	7100
GACTCCTTCG	ATCCGCTTGT	GGCAGAGGAG	GATGAGCGGG	AGGTCTCCGT	7150
ACCTGCAGAA	ATTCTGCGGA	AGTCTCGGAG	ATTCGCCCGG	GCCCTGCCCG	7200
TCTGGGCGCG	GCCGGACTAC	AACCCCCCGC	TAGTAGAGAC	GTGGAAAAAG	7250
CCTGACTACG	AACCACCTGT	GGTCCATGGC	TGCCCGCTAC	CACCTCCACG	7300
GTCCCCTCCT	GTGCCTCCGC	CTCGGAAAAA	GCGTACGGTG	GTCCTCACCG	7350
AATCAACCCT	ATCTACTGCC	TTGGCCGAGC	TTGCCACCAA	AAGTTTTGGC	7400
AGCTCCTCAA	CTTCCGGCAT	TACGGGCGAC	AATACGACAA	CATCCTCTGA	7450
GCCCGCCCCT	TCTGGCTGCC	CCCCCGACTC	CGACGTTGAG	TCCTATTCTT	7500
CCATGCCCCC	CCTGGAGGGG	GAGCCTGGGG	ATCCGGATCT	CAGCGACGGG	7550
TCATGGTCGA	CGGTCAGTAG	TGGGGCCGAC	ACGGAAGATG	TCGTGTGCTG	7600

FIG. 6D

H77C

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
CTCAATGTCT	TATTCCTGGA	CAGGCGCACT	CGTCACCCCG	TGCGCTGCGG	7650
AAGAACAAAA	ACTGCCCATC	AACGCACTGA	GCAACTCGTT	GCTACGCCAT	7700
CACAATCTGG	TGTATTCCAC	CACTTCACGC	AGTGCTTGCC	AAAGGCAGAA	7750
GAAAGTCACA	TTTGACAGAC	TGCAAGTTCT	GGACAGCCAT	TACCAGGACG	7800
TGCTCAAGGA	GGTCAAAGCA	GCGGCGTCAA	AAGTGAAGGC	TAACTTGCTA	7850
TCCGTAGAGG	AAGCTTGCAG	CCTGACGCCC	CCACATTCAG	CCAAATCCAA	7900
GTTTGGCTAT	GGGGCAAAAG	ACGTCCGTTG	CCATCCCAGA	AAGGCCGTAG	7950
CCCACATCAA	CTCCGTGTGG	AAAGACCTTC	TGGAAGACAG	TGTAACACCA	8000
ATAGACACTA	CCATCATGGC	CAAGAACGAG	GTTTTCTGCG	TTCAGCCTGA	8050
GAAGGGGGGT	CGTAAGCCAG	CTCGTCTCAT	CGTGTTCCCC	GACCTGGGCG	8100
TGCGCGTGTG	CGAGAAGATG	GCCCTGTACG	ACGTGGTTAG	CAAGCTCCCC	8150
CTGGCCGTGA	TGGGAAGCTC	CTACGGATTC	CAATACTCAC	CAGGACAGCG	8200
GGTTGAATTC	CTCGTGCAAG	CGTGGAAGTC	CAAGAAGACC	CCGATGGGGT	8250
TCTCGTATGA	TACCCGCTGT	TTTGACTCCA	CAGTCACTGA	GAGCGACATC	8300
CGTACGGAGG	AGGCAATTTA	CCAATGTTGT	GACCTGGACC	CCCAAGCCCG	8350
CGTGGCCATC	AAGTCCCTCA	CTGAGAGGCT	TTATGTTGGG	GGCCCTCTTA	8400
CCAATTCAAG	GGGGGAAAAC	TGCGGCTACC	GCAGGTGCCG	CGCGAGCGGC	8450
GTACTGACAA	CTAGCTGTGG	TAACACCCTC	ACTTGCTACA	TCAAGGCCCG	8500
GGCAGCCTGT	CGAGCCGCAG	GGCTCCAGGA	CTGCACCATG	CTCGTGTGTG	8550
GCGACGACTT	AGTCGTTATC	TGTGAAAGTG	CGGGGGTCCA	GGAGGACGCG	8600
GCGAGCCTGA	GAGCCTTCAC	GGAGGCTATG	ACCAGGTACT	CCGCCCCCCC	8650
CGGGGACCCC	CCACAACCAG	AATACGACTT	GGAGCTTATA	ACATCATGCT	8700
CCTCCAACGT	GTCAGTCGCC	CACGACGGCG	CTGGAAAGAG	GGTCTACTAC	8750
CTTACCCGTG	ACCCTACAAC	CCCCCTCGCG	AGAGCCGCGT	GGGAGACAGC	8800
AAGACACACT	CCAGTCAATT	CCTGGCTAGG	CAACATAATC	ATGTTTGCCC	8850
CCACACTGTG	GGCGAGGATG	ATACTGATGA	CCCATTTCTT	TAGCGTCCTC	8900
ATAGCCAGGG	ATCAGCTTGA	ACAGGCTCTT	AACTGTGAGA	TCTACGGAGC	8950
CTGCTACTCC	ATAGAACCAC	TGGATCTACC	TCCAATCATT	CAAAGACTCC	9000
ATGGCCTCAG	CGCATTTTCA	CTCCACAGTT	ACTCTCCAGG	TGAAATCAAT	9050
AGGGTGGCCG	CATGCCTCAG	AAAACTTGGG	GTCCCGCCCT	TGCGAGCTTG	9100
GAGACACCGG	GCCCGGAGCG	TCCGCGCTAG	GCTTCTGTCC	AGAGGAGGCA	9150
GGGCTGCCAT	ATGTGGCAAG	TACCTCTTCA	ACTGGGCAGT	AAGAACAAAG	9200
CTCAAACTCA	CTCCAATAGC	GGCCGCTGGC	CGGCTGGACT	TGTCCGGTTG	9250
GTTCACGGCT	GGCTACAGCG	GGGGAGACAT	TTATCACAGC	GTGTCTCATG	9300
CCCGGCCCCG	CTGGTTCTGG	TTTTGCCTAC	TCCTGCTCGC	TGCAGGGGTA	9350
GGCATCTACC	TCCTCCCCAA	CCGATGAAGG	TTGGGGTAAA	CACTCCGGCC	9400
TCTTAAGCCA	TTTCCTGTTT	TTTTTTTTTT	TTTTTTTTTT	TTTTTCTTTT	9450
TTTTTTTCTT	TCCTTTCCTT	CTTTTTTTCC	TTTCTTTTTC	CCTTCTTTAA	9500

FIG. 6E

H77C

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
TGGTGGCTCC	ATCTTAGCCC	TAGTCACGGC	TAGCTGTGAA	AGGTCCGTGA	9550
GCCGCATGAC	TGCAGAGAGT	GCTGATACTG	GCCTCTCTGC	AGATCATGT	9599

FIG. 6F

H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
MSTNPKPQRK	TKRNTNRRPQ	DVKFPGGGQI	VGGVYLLPRR	GPRLGVRATR	50
KTSERSQPRG	RRQPIPKARR	PEGRTWAQPG	YPWPLYGNEG	CGWAGWLLSP	100
RGSRPSWGPT	DPRRRSRNLG	KVIDTLTCGF	ADLMGYIPLV	GAPLGGAARA	150
LAHGVRVLED	GVNYATGNLP	GCSFSIFLLA	LLSCLTVPAS	AYQVRNSSGL	200
YHVTNDCPNS	SIVYEAADAI	LHTPGCVPCV	REGNASRCWV	AVTPTVATRD	250
GKLPTTQLRR	HIDLLVGSAT	LCSALYVGDL	CGSVFLVGQL	FTFSPRRHWT	300
TQDCNCSIYP	GHITGHRMAW	DMMMNWSPTA	ALVVAQLLRI	PQAIMDMIAG	350
AHWGVLAGIA	YFSMVGNWAK	VLVVLLLFAG	VDAETHVTGG	NAGRTTAGLV	400
GLLTPGAKQN	IQLINTNGSW	HINSTALNCN	ESLNTGWLAG	LFYQHKFNSS	450
GCPERLASCR	RLTDFAQGWG	PISYANGSGL	DERPYCWHYP	PRPCGIVPAK	500
SVCGPVYCFT	PSPVVVGTTD	RSGAPTYSWG	ANDTDVFVLN	NTRPPLGNWF	550
GCTWMNSTGF	TKVCGAPPCV	IGGVGNNTLL	CPTDCFRKHP	EATYSRCGSG	600
PWITPRCMVD	YPYRLWHYPC	TINYTIFKVR	MYVGGVEHRL	EAACNWTRGE	650
RCDLEDRDRS	ELSPLLLSTT	QWQVLPCSFT	TLPALSTGLI	HLHQNIVDVQ	700
YLYGVGSSIA	SWAIKWEYVV	LLFLLLADAR	VCSCLWMMLL	ISQAEAALEN	750
LVILNAASLA	GTHGLVSFLV	FFCFAWYLKG	RWVPGAVYAL	YGMWPLLLLL	800
LALPQRAYAL	DTEVAASCGG	VVLVGLMALT	LSPYYKRYIS	WCMWWLQYFL	850
TRVEAQLHVW	VPPLNVRGGR	DAVILLMCVV	HPTLVFDITK	LLLAIFGPLW	900
ILQASLLKVP	YFVRVQGLLR	ICALARKIAG	GHYVQMAIIK	LGALTGTYVY	950
NHLTPLRDWA	HNGLRDLAVA	VEPVVFSRME	TKLITWGADT	AACGDIINGL	1000
PVSARRGQEI	LLGPADGMVS	KGWRLLAPIT	AYAQQTRGLL	GCIITSLTGR	1050
DKNQVEGEVQ	IVSTATQTFL	ATCINGVCWT	VYHGAGTRTI	ASPKGPVIQM	1100
YTNVDQDLVG	WPAPQGSRSL	TPCTCGSSDL	YLVTRHADVI	PVRRRGDSRG	1150
SLLSPRPISY	LKGSSGGPLL	CPAGHAVGLF	RAAVCTRGVA	KAVDFIPVEN	1200
LGTTMRSPVF	TDNSSPPAVP	QSFQVAHLHA	PTGSGKSTKV	PAAYAAQGYK	1250
VLVLNPSVAA	TLGFGAYMSK	AHGVDPNIRT	GVRTITTGSP	ITYSTYGKFL	1300
ADGGCSGGAY	DIIICDECHS	TDATSILGIG	TVLDQAETAG	ARLVVLATAT	1350
PPGSVTVSHP	NIEEVALSTT	GEIPFYGKAI	PLEVIKGGRH	LIFCHSKKKC	1400
DELAAKLVAL	GINAVAYYRG	LDVSVIPTSG	DVVVVSTDAL	MTGFTGDFDS	1450
VIDCNTCVTQ	TVDFSLDPTF	TIETTTLPQD	AVSRTQRRGR	TGRGKPGIYR	1500
FVAPGERPSG	MFDSSVLCEC	YDAGCAWYEL	TPAETTVRLR	AYMNTPGLPV	1550
CQDHLEFWEG	VFTGLTHIDA	HFLSQTKQSG	ENFPYLVAYQ	ATVCARAQAP	1600
PPSWDQMWKC	LIRLKPTLHG	PTPLLYRLGA	VQNEVTLTHP	ITKYIMTCMS	1650
ADLEVVTSTW	VLVGGVLAAL	AAYCLSTGCV	VIVGRIVLSG	KPAIIPDREV	1700
LYQEFDEMEE	CSQHLPYIEQ	GMMLAEQFKQ	KALGLLQTAS	RHAEVITPAV	1750
QTNWQKLEVF	WAKHMWNFIS	GIQYLAGLST	LPGNPAIASL	MAFTAAVTSP	1800
LTTGQTLLFN	ILGGWVAAQL	AAPGAATAFV	GAGLAGAAIG	SVGLGKVLVD	1850
ILAGYGAGVA	GALVAFKIMS	GEVPSTEDLV	NLLPAILSPG	ALVVGVVCAA	1900

FIG. 6G

H77C

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        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
ILRRHVGPGE GAVQWMNRLI AFASRGNHVS PTHYVPESDA AARVTAILSS   1950
LTVTQLLRRL HQWISSECTT PCSGSWLRDI WDWICEVLSD FKTWLKAKLM   2000
PQLPGIPFVS CQRGYRGVWR GDGIMHTRCH CGAEITGHVK NGTMRIVGPR   2050
TCRNMWSGTF PINAYTTGPC TPLPAPNYKF ALWRVSAEEY VEIRRVGDFH   2100
YVSGMTTDNL KCPCQIPSPE FFTELDGVRL HRFAPPCKPL LREEVSFRVG   2150
LHEYPVGSQL PCEPEPDVAV LTSMLTDPSH ITAEAAGRRL ARGSPPSMAS   2200
SSASQLSAPS LKATCTANHD SPDAELIEAN LLWRQEMGGN ITRVESENKV   2250
VILDSFDPLV AEEDEREVSV PAEILRKSRR FARALPVWAR PDYNPPLVET   2300
WKKPDYEPPV VHGCPLPPPR SPPVPPPRKK RTVVLTESTL STALAELATK   2350
SFGSSSTSGI TGDNTTTSSE PAPSGCPPDS DVESYSSMPP LEGEPGDPDL   2400
SDGSWSTVSS GADTEDVVCC SMSYSWTGAL VTPCAAEEQK LPINALSNSL   2450
LRHHNLVYST TSRSACQRQK KVTFDRLQVL DSHYQDVLKE VKAAASKVKA   2500
NLLSVEEACS LTPPHSAKSK FGYGAKDVRC HARKAVAHIN SVWKDLLEDS   2550
VTPIDTTIMA KNEVFCVQPE KGGRKPARLI VFPDLGVRVC EKMALYDVVS   2600
KLPLAVMGSS YGFQYSPGQR VEFLVQAWKS KKTPMGFSYD TRCFDSTVTE   2650
SDIRTEEAIY QCCDLDPQAR VAIKSLTERL YVGGPLTNSR GENCGYRRCR   2700
ASGVLTTSCG NTLTCYIKAR AACRAAGLQD CTMLVCGDDL VVICESAGVQ   2750
EDAASLRAFT EAMTRYSAPP GDPPQPEYDL ELITSCSSNV SVAHDGAGKR   2800
VYYLTRDPTT PLARAAWETA RHTPVNSWLG NIIMFAPTLW ARMILMTHFF   2850
SVLIARDQLE QALNCEIYGA CYSIEPLDLP PIIQRLHGLS AFSLHSYSPG   2900
EINRVAACLR KLGVPPLRAW RHRARSVRAR LLSRGGRAAI CGKYLFNWAV   2950
RTKLKLTPIA AAGRLDLSGW FTAGYSGGDI YHSVSHARPR WFWFCLLLLA   3000
AGVGIYLLPN R                                             3011
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FIG. 6H

HC-J4

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
GCCAGCCCCC	TGATGGGGGC	GACACTCCAC	CATGAATCAC	TCCCCTGTGA	50
GGAACTACTG	TCTTCACGCA	GAAAGCGTCT	AGCCATGGCG	TTAGTATGAG	100
TGTCGTGCAG	CCTCCAGGAC	CCCCCCTCCC	GGGAGAGCCA	TAGTGGTCTG	150
CGGAACCGGT	GAGTACACCG	GAATTGCCAG	GACGACCGGG	TCCTTTCTTG	200
GATCAACCCG	CTCAATGCCT	GGAGATTTGG	GCGTGCCCCC	GCGAGACTGC	250
TAGCCGAGTA	GTGTTGGGTC	GCGAAAGGCC	TTGTGGTACT	GCCTGATAGG	300
GTGCTTGCGA	GTGCCCCGGG	AGGTCTCGTA	GACCGTGCAC	CATGAGCACG	350
AATCCTAAAC	CTCAAAGAAA	AACCAAACGT	AACACCAACC	GCCGCCCACA	400
GGACGTCAAG	TTCCCGGGCG	GTGGTCAGAT	CGTTGGTGGA	GTTTACCTGT	450
TGCCGCGCAG	GGGCCCCAGG	TTGGGTGTGC	GCGCGACTAG	GAAGGCTTCC	500
GAGCGGTCGC	AACCTCGTGG	AAGGCGACAA	CCTATCCCAA	AGGCTCGCCG	550
ACCCGAGGGC	AGGGCCTGGG	CTCAGCCCGG	GTACCCTTGG	CCCCTCTATG	600
GCAATGAGGG	CCTGGGGTGG	GCAGGATGGC	TCCTGTCACC	CCGCGGCTCC	650
CGGCCTAGTT	GGGGCCCCAC	GGACCCCCGG	CGTAGGTCGC	GTAACTTGGG	700
TAAGGTCATC	GATACCCTTA	CATGCGGCTT	CGCCGATCTC	ATGGGGTACA	750
TTCCGCTCGT	CGGCGCCCCC	CTAGGGGGCG	CTGCCAGGGC	CTTGGCACAC	800
GGTGTCCGGG	TTCTGGAGGA	CGGCGTGAAC	TATGCAACAG	GGAACTTGCC	850
CGGTTGCTCT	TTCTCTATCT	TCCTCTTGGC	TCTGCTGTCC	TGTTTGACCA	900
TCCCAGCTTC	CGCTTATGAA	GTGCGCAACG	TGTCCGGGAT	ATACCATGTC	950
ACGAACGACT	GCTCCAACTC	AAGCATTGTG	TATGAGGCAG	CGGACGTGAT	1000
CATGCATACT	CCCGGGTGCG	TGCCCTGTGT	TCAGGAGGGT	AACAGCTCCC	1050
GTTGCTGGGT	AGCGCTCACT	CCCACGCTCG	CGGCCAGGAA	TGCCAGCGTC	1100
CCCACTACGA	CAATACGACG	CCACGTCGAC	TTGCTCGTTG	GGACGGCTGC	1150
TTTCTGCTCC	GCTATGTACG	TGGGGGATCT	CTGCGGATCT	ATTTTCCTCG	1200
TCTCCCAGCT	GTTCACCTTC	TCGCCTCGCC	GGCATGAGAC	AGTGCAGGAC	1250
TGCAACTGCT	CAATCTATCC	CGGCCATGTA	TCAGGTCACC	GCATGGCTTG	1300
GGATATGATG	ATGAACTGGT	CACCTACAAC	AGCCCTAGTG	GTGTCGCAGT	1350
TGCTCCGGAT	CCCACAAGCT	GTCGTGGACA	TGGTGGCGGG	GGCCCACTGG	1400
GGAGTCCTGG	CGGGCCTTGC	CTACTATTCC	ATGGTAGGGA	ACTGGGCTAA	1450
GGTTCTGATT	GTGGCGCTAC	TCTTTGCCGG	CGTTGACGGG	GAGACCCACA	1500
CGACGGGGAG	GGTGGCCGGC	CACACCACCT	CCGGGTTCAC	GTCCCTTTTC	1550
TCATCTGGGG	CGTCTCAGAA	AATCCAGCTT	GTGAATACCA	ACGGCAGCTG	1600
GCACATCAAC	AGGACTGCCC	TAAATTGCAA	TGACTCCCTC	CAAACTGGGT	1650
TCTTTGCCGC	GCTGTTTTAC	GCACACAAGT	TCAACTCGTC	CGGGTGCCCG	1700
GAGCGCATGG	CCAGCTGCCG	CCCCATTGAC	TGGTTCGCCC	AGGGGTGGGG	1750
CCCCATCACC	TATACTAAGC	CTAACAGCTC	GGATCAGAGG	CCTTATTGCT	1800
GGCATTACGC	GCCTCGACCG	TGTGGTGTCG	TACCCGCGTC	GCAGGTGTGT	1850
GGTCCAGTGT	ATTGTTTCAC	CCCAAGCCCT	GTTGTGGTGG	GGACCACCGA	1900

FIG. 7A

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCGTTCCGGT	GTCCCTACGT	ATAGCTGGGG	GGAGAATGAG	ACAGACGTGA	1950
TGCTCCTCAA	CAACACGCGT	CCGCCACAAG	GCAACTGGTT	CGGCTGTACA	2000
TGGATGAATA	GTACTGGGTT	CACTAAGACG	TGCGGAGGTC	CCCCGTGTAA	2050
CATCGGGGGG	GTCGGTAACC	GCACCTTGAT	CTGCCCCACG	GACTGCTTCC	2100
GGAAGCACCC	CGAGGCTACT	TACACAAAAT	GTGGCTCGGG	GCCCTGGTTG	2150
ACACCTAGGT	GCCTAGTAGA	CTACCCATAC	AGGCTTTGGC	ACTACCCCTG	2200
CACTCTCAAT	TTTTCCATCT	TTAAGGTTAG	GATGTATGTG	GGGGGCGTGG	2250
AGCACAGGCT	CAATGCCGCA	TGCAATTGGA	CTCGAGGAGA	GCGCTGTAAC	2300
TTGGAGGACA	GGGATAGGTC	AGAACTCAGC	CCGCTGCTGC	TGTCTACAAC	2350
AGAGTGGCAG	ATACTGCCCT	GTGCTTTCAC	CACCCTACCG	GCTTTATCCA	2400
CTGGTTTGAT	CCATCTCCAT	CAGAACATCG	TGGACGTGCA	ATACCTGTAC	2450
GGTGTAGGGT	CAGCGTTTGT	CTCCTTTGCA	ATCAAATGGG	AGTACATCCT	2500
GTTGCTTTTC	CTTCTCCTGG	CAGACGCGCG	CGTGTGTGCC	TGCTTGTGGA	2550
TGATGCTGCT	GATAGCCCAG	GCTGAGGCCG	CCTTAGAGAA	CTTGGTGGTC	2600
CTCAATGCGG	CGTCCGTGGC	CGGAGCGCAT	GGTATTCTCT	CCTTTCTTGT	2650
GTTCTTCTGC	GCCGCCTGGT	ACATTAAGGG	CAGGCTGGCT	CCTGGGGCGG	2700
CGTATGCTTT	TTATGGCGTA	TGGCCGCTGC	TCCTGCTCCT	ACTGGCGTTA	2750
CCACCACGAG	CTTACGCCTT	GGACCGGGAG	ATGGCTGCAT	CGTGCGGGGG	2800
TGCGGTTCTT	GTAGGTCTGG	TATTCTTGAC	CTTGTCACCA	TACTACAAAG	2850
TGTTTCTCAC	TAGGCTCATA	TGGTGGTTAC	AATACTTTAT	CACCAGAGCC	2900
GAGGCGCACA	TGCAAGTGTG	GGTCCCCCCC	CTCAACGTTC	GGGGAGGCCG	2950
CGATGCCATC	ATCCTCCTCA	CGTGTGCGGT	TCATCCAGAG	TTAATTTTTG	3000
ACATCACCAA	ACTCCTGCTC	GCCATACTCG	GCCCGCTCAT	GGTGCTCCAG	3050
GCTGGCATAA	CGAGAGTGCC	GTACTTCGTG	CGCGCTCAAG	GGCTCATTCG	3100
TGCATGCATG	TTAGTGCGAA	AAGTCGCCGG	GGGTCATTAT	GTCCAAATGG	3150
TCTTCATGAA	GCTGGCGCCG	CTGACAGGTA	CGTACGTTTA	TAACCATCTT	3200
ACCCCACTGC	GGGACTGGGC	CCACGCGGGC	CTACGAGACC	TTGCGGTGGC	3250
GGTAGAGCCC	GTCGTCTTCT	CCGCCATGGA	GACCAAGGTC	ATCACCTGGG	3300
GAGCAGACAC	CGCTGCGTGT	GGGGACATCA	TCTTGGGTCT	ACCCGTCTCC	3350
GCCCGAAGGG	GGAAGGAGAT	ATTTTTGGGA	CCGGCTGATA	GTCTCGAAGG	3400
GCAAGGGTGG	CGACTCCTTG	CGCCCATCAC	GGCCTACTCC	CAACAAACGC	3450
GGGGCGTACT	TGGTTGCATC	ATCACTAGCC	TCACAGGCCG	GGACAAGAAC	3500
CAGGTCGAAG	GGGAGGTTCA	AGTGGTTTCT	ACCGCAACAC	AATCTTTCCT	3550
GGCGACCTGC	ATCAACGGCG	TGTGCTGGAC	TCTCTACCAT	GGCGCTGGCT	3600
CGAAGACCCT	AGCCGGTCCA	AAAGGTCCAA	TCACCCAAAT	GTACACCAAT	3650
GTAGACCTGG	ACCTCGTCGG	CTGGCAGGCG	CCCCCCGGGG	CGCGCTCCAT	3700
GACACCATGC	AGCTGTGGCA	GCTCGGACCT	TTACTTGGTC	ACGAGACATG	3750
CTGATGTCAT	TCCGGTGCGC	CGGCGAGGCG	ACAGCAGGGG	AAGTCTACTC	3800

FIG. 7B

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HC-J4

10 1234567890	20 1234567890	30 1234567890	40 1234567890	50 1234567890	
TCCCCCAGGC	CCGTCTCCTA	CCTGAAAGGC	TCCTCGGGTG	GTCCATTGCT	3850
TTGCCCTTCG	GGGCACGTCG	TGGGCGTCTT	CCGGGCTGCT	GTGTGCACCC	3900
GGGGGGTCGC	GAAGGCGGTG	GACTTCATAC	CCGTTGAGTC	TATGGAAACT	3950
ACCATGCGGT	CTCCGGTCTT	CACAGACAAC	TCAACCCCCC	CGGCTGTACC	4000
GCAGACATTC	CAAGTGGCAC	ATCTGCACGC	TCCTACTGGC	AGCGGCAAGA	4050
GCACCAAAGT	GCCGGCTGCG	TATGCAGCCC	AAGGGTACAA	GGTGCTCGTC	4100
CTGAACCCGT	CCGTTGCCGC	CACCTTAGGG	TTTGGGGCGT	ATATGTCCAA	4150
GGCACACGGT	ATCGACCCTA	ACATCAGAAC	TGGGGTAAGG	ACCATTACCA	4200
CGGGCGGCTC	CATTACGTAC	TCCACCTATG	GCAAGTTCCT	TGCCGACGGT	4250
GGCTGTTCTG	GGGGCGCCTA	TGACATCATA	ATATGTGATG	AGTGCCACTC	4300
AACTGACTCG	ACTACCATCT	TGGGCATCGG	CACAGTCCTG	GACCAAGCGG	4350
AGACGGCTGG	AGCGCGGCTC	GTCGTGCTCG	CCACCGCTAC	ACCTCCGGGA	4400
TCGGTTACCG	TGCCACACCC	CAATATCGAG	GAAATAGGCC	TGTCCAACAA	4450
TGGAGAGATC	CCCTTCTATG	GCAAAGCCAT	CCCCATTGAG	GCCATCAAGG	4500
GGGGGAGGCA	TCTCATTTTC	TGCCATTCCA	AGAAGAAATG	TGACGAGCTC	4550
GCCGCAAAGC	TGACAGGCCT	CGGACTGAAC	GCTGTAGCAT	ATTACCGGGG	4600
CCTTGATGTG	TCCGTCATAC	CGCCTATCGG	AGACGTCGTT	GTCGTGGCAA	4650
CAGACGCTCT	AATGACGGGT	TTCACCGGCG	ATTTTGACTC	AGTGATCGAC	4700
TGCAATACAT	GTGTCACCCA	GACAGTCGAC	TTCAGCTTGG	ATCCCACCTT	4750
CACCATTGAG	ACGACGACCG	TGCCCCAAGA	CGCGGTGTCG	CGCTCGCAAC	4800
GGCGAGGTAG	AACTGGCAGG	GGTAGGAGTG	GCATCTACAG	GTTTGTGACT	4850
CCAGGAGAAC	GGCCCTCGGG	CATGTTCGAT	TCTTCGGTCC	TGTGTGAGTG	4900
CTATGACGCG	GGCTGTGCTT	GGTATGAGCT	CACGCCCGCT	GAGACCTCGG	4950
TTAGGTTGCG	GGCTTACCTA	AATACACCAG	GGTTGCCCGT	CTGCCAGGAC	5000
CATCTGGAGT	TCTGGGAGAG	CGTCTTCACA	GGCCTCACCC	ACATAGATGC	5050
CCACTTCCTG	TCCCAGACTA	AACAGGCAGG	AGACAACTTT	CCTTACCTGG	5100
TGGCATATCA	AGCTACAGTG	TGCGCCAGGG	CTCAAGCTCC	ACCTCCATCG	5150
TGGGACCAAA	TGTGGAAGTG	TCTCATACGG	CTGAAACCTA	CACTGCACGG	5200
GCCAACACCC	CTGCTGTATA	GGCTAGGAGC	CGTCCAAAAT	GAGGTCATCC	5250
TCACACACCC	CATAACTAAA	TACATCATGG	CATGCATGTC	GGCTGACCTG	5300
GAGGTCGTCA	CTAGCACCTG	GGTGCTGGTA	GGCGGAGTCC	TTGCAGCTTT	5350
GGCCGCATAC	TGCCTGACGA	CAGGCAGTGT	GGTCATTGTG	GGCAGGATCA	5400
TCTTGTCCGG	GAAGCCAGCT	GTCGTTCCCG	ACAGGGAAGT	CCTCTACCAG	5450
GAGTTCGATG	AGATGGAAGA	GTGTGCCTCA	CAACTTCCTT	ACATCGAGCA	5500
GGGAATGCAG	CTCGCCGAGC	AATTCAAGCA	AAAGGCGCTC	GGGTTGTTGC	5550
AAACGGCCAC	CAAGCAAGCG	GAGGCTGCTG	CTCCCGTGGT	GGAGTCCAAG	5600
TGGCGAGCCC	TTGAGACCTT	CTGGGCGAAG	CACATGTGGA	ATTTCATCAG	5650
CGGAATACAG	TACCTAGCAG	GCTTATCCAC	TCTGCCTGGA	AACCCCGCGA	5700

FIG. 7C

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TAGCATCATT	GATGGCATTT	ACAGCTTCTA	TCACTAGCCC	GCTCACCACC	5750
CAAAACACCC	TCCTGTTTAA	CATCTTGGGG	GGATGGGTGG	CTGCCCAACT	5800
CGCTCCTCCC	AGCGCTGCGT	CAGCTTTCGT	GGGCGCCGGC	ATCGCCGGAG	5850
CGGCTGTTGG	CAGCATAGGC	CTTGGGAAGG	TGCTCGTGGA	CATCTTGGCG	5900
GGCTATGGGG	CAGGGGTAGC	CGGCGCACTC	GTGGCCTTTA	AGGTCATGAG	5950
CGGCGAGGTG	CCCTCCACCG	AGGACCTGGT	CAACTTACTC	CCTGCCATCC	6000
TCTCTCCTGG	TGCCCTGGTC	GTCGGGGTCG	TGTGCGCAGC	AATACTGCGT	6050
CGGCACGTGG	GCCCGGGAGA	GGGGGCTGTG	CAGTGGATGA	ACCGGCTGAT	6100
AGCGTTCGCT	TCGCGGGGTA	ACCACGTCTC	CCCTACGCAC	TATGTGCCTG	6150
AGAGCGACGC	TGCAGCACGT	GTCACTCAGA	TCCTCTCTAG	CCTTACCATC	6200
ACTCAACTGC	TGAAGCGGCT	CCACCAGTGG	ATTAATGAGG	ACTGCTCTAC	6250
GCCATGCTCC	GGCTCGTGGC	TAAGGGATGT	TTGGGATTGG	ATATGCACGG	6300
TGTTGACTGA	CTTCAAGACC	TGGCTCCAGT	CCAAACTCCT	GCCGCGGTTA	6350
CCGGGAGTCC	CTTTCCTGTC	ATGCCAACGC	GGGTACAAGG	GAGTCTGGCG	6400
GGGGGACGGC	ATCATGCAAA	CCACCTGCCC	ATGCGGAGCA	CAGATCGCCG	6450
GACATGTCAA	AAACGGTTCC	ATGAGGATCG	TAGGGCCTAG	AACCTGCAGC	6500
AACACGTGGC	ACGGAACGTT	CCCCATCAAC	GCATACACCA	CGGGACCTTG	6550
CACACCCTCC	CCGGCGCCCA	ACTATTCCAG	GGCGCTATGG	CGGGTGGCTG	6600
CTGAGGAGTA	CGTGGAGGTT	ACGCGTGTGG	GGGATTTCCA	CTACGTGACG	6650
GGCATGACCA	CTGACAACGT	AAAGTGCCCA	TGCCAGGTTC	CGGCCCCCGA	6700
ATTCTTCACG	GAGGTGGATG	GAGTGCGGTT	GCACAGGTAC	GCTCCGGCGT	6750
GCAAACCTCT	TCTACGGGAG	GACGTCACGT	TCCAGGTCGG	GCTCAACCAA	6800
TACTTGGTCG	GGTCGCAGCT	CCCATGCGAG	CCCGAACCGG	ACGTAACAGT	6850
GCTTACTTCC	ATGCTCACCG	ATCCCTCCCA	CATTACAGCA	GAGACGGCTA	6900
AGCGTAGGCT	GGCTAGAGGG	TCTCCCCCCT	CTTTAGCCAG	CTCATCAGCT	6950
AGCCAGTTGT	CTGCGCCTTC	TTTGAAGGCG	ACATGCACTA	CCCACCATGA	7000
CTCCCCGGAC	GCTGACCTCA	TCGAGGCCAA	CCTCTTGTGG	CGGCAGGAGA	7050
TGGGCGGAAA	CATCACTCGC	GTGGAGTCAG	AGAATAAGGT	AGTAATTCTG	7100
GACTCTTTCG	AACCGCTTCA	CGCGGAGGGG	GATGAGAGGG	AGATATCCGT	7150
CGCGGCGGAG	ATCCTGCGAA	AATCCAGGAA	GTTCCCCTCA	GCGTTGCCCA	7200
TATGGGCACG	CCCGGACTAC	AATCCTCCAC	TGCTAGAGTC	CTGGAAGGAC	7250
CCGGACTACG	TCCCTCCGGT	GGTACACGGA	TGCCCATTGC	CACCTACCAA	7300
GGCTCCTCCA	ATACCACCTC	CACGGAGAAA	GAGGACGGTT	GTCCTGACAG	7350
AATCCAATGT	GTCTTCTGCC	TTGGCGGAGC	TCGCCACTAA	GACCTTCGGT	7400
AGCTCCGGAT	CGTCGGCCGT	TGATAGCGGC	ACGGCGACCG	CCCTTCCTGA	7450
CCTGGCCTCC	GACGACGGTG	ACAAAGGATC	CGACGTTGAG	TCGTACTCCT	7500
CCATGCCCCC	CCTTGAAGGG	GAGCCGGGGG	ACCCCGATCT	CAGCGACGGG	7550
TCTTGGTCTA	CCGTGAGTGA	GGAGGCTAGT	GAGGATGTCG	TCTGCTGCTC	7600

FIG. 7D

HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
AATGTCCTAT	ACGTGGACAG	GCGCCCTGAT	CACGCCATGC	GCTGCGGAGG	7650
AAAGTAAGCT	GCCCATCAAC	CCGTTGAGCA	ACTCTTTGCT	GCGTCACCAC	7700
AACATGGTCT	ACGCCACAAC	ATCCCGCAGC	GCAAGCCTCC	GGCAGAAGAA	7750
GGTCACCTTT	GACAGATTGC	AAGTCCTGGA	TGATCATTAC	CGGGACGTAC	7800
TCAAGGAGAT	GAAGGCGAAG	GCGTCCACAG	TTAAGGCTAA	GCTTCTATCT	7850
ATAGAGGAGG	CCTGCAAGCT	GACGCCCCCA	CATTCGGCCA	AATCCAAATT	7900
TGGCTATGGG	GCAAAGGACG	TCCGGAACCT	ATCCAGCAGG	GCCGTTAACC	7950
ACATCCGCTC	CGTGTGGGAG	GACTTGCTGG	AAGACACTGA	AACACCAATT	8000
GACACCACCA	TCATGGCAAA	AAGTGAGGTT	TTCTGCGTCC	AACCAGAGAA	8050
GGGAGGCCGC	AAGCCAGCTC	GCCTTATCGT	ATTCCCAGAC	CTGGGAGTTC	8100
GTGTATGCGA	GAAGATGGCC	CTTTACGACG	TGGTCTCCAC	CCTTCCTCAG	8150
GCCGTGATGG	GCTCCTCATA	CGGATTTCAA	TACTCCCCCA	AGCAGCGGGT	8200
CGAGTTCCTG	GTGAATACCT	GGAAATCAAA	GAAATGCCCT	ATGGGCTTCT	8250
CATATGACAC	CCGCTGTTTT	GACTCAACGG	TCACTGAGAG	TGACATTCGT	8300
GTTGAGGAGT	CAATTTACCA	ATGTTGTGAC	TTGGCCCCCG	AGGCCAGACA	8350
GGCCATAAGG	TCGCTCACAG	AGCGGCTTTA	CATCGGGGGT	CCCCTGACTA	8400
ACTCAAAAGG	GCAGAACTGC	GGTTATCGCC	GGTGCCGCGC	AAGTGGCGTG	8450
CTGACGACTA	GCTGCGGTAA	TACCCTCACA	TGTTACTTGA	AGGCCACTGC	8500
AGCCTGTCGA	GCTGCAAAGC	TCCAGGACTG	CACGATGCTC	GTGAACGGAG	8550
ACGACCTTGT	CGTTATCTGT	GAAAGCGCGG	GAACCCAGGA	GGATGCGGCG	8600
GCCCTACGAG	CCTTCACGGA	GGCTATGACT	AGGTATTCCG	CCCCCCCCGG	8650
GGATCCGCCC	CAACCAGAAT	ACGACCTGGA	GCTGATAACA	TCATGTTCCT	8700
CCAATGTGTC	AGTCGCGCAC	GATGCATCTG	GCAAAAGGGT	ATACTACCTC	8750
ACCCGTGACC	CCACCACCCC	CCTTGCACGG	GCTGCGTGGG	AGACAGCTAG	8800
ACACACTCCA	ATCAACTCTT	GGCTAGGCAA	TATCATCATG	TATGCGCCCA	8850
CCCTATGGGC	AAGGATGATT	CTGATGACTC	ACTTTTTCTC	CATCCTTCTA	8900
GCTCAAGAGC	AACTTGAAAA	AGCCCTGGAT	TGTCAGATCT	ACGGGGCTTG	8950
CTACTCCATT	GAGCCACTTG	ACCTACCTCA	GATCATTGAA	CGACTCCATG	9000
GTCTTAGCGC	ATTTACACTC	CACAGTTACT	CTCCAGGTGA	GATCAATAGG	9050
GTGGCTTCAT	GCCTCAGGAA	ACTTGGGGTA	CCACCCTTGC	GAACCTGGAG	9100
ACATCGGGCC	AGAAGTGTCC	GCGCTAAGCT	ACTGTCCCAG	GGGGGGAGGG	9150
CCGCCACTTG	TGGCAGATAC	CTCTTTAACT	GGGCAGTAAG	GACCAAGCTT	9200
AAACTCACTC	CAATCCCGGC	CGCGTCCCAG	CTGGACTTGT	CTGGCTGGTT	9250
CGTCGCTGGT	TACAGCGGGG	GAGACATATA	TCACAGCCTG	TCTCGTGCCC	9300
GACCCCGCTG	GTTTCCGTTG	TGCCTACTCC	TACTTTCTGT	AGGGGTAGGC	9350
ATTTACCTGC	TCCCCAACCG	ATGAACGGGG	AGCTAACCAC	TCCAGGCCTT	9400
AAGCCATTTC	CTGTTTTTTT	TTTTTTTTTT	TTTTTTTTTT	TCTTTTTTTT	9450
TTTCTTTCCT	TTCCTTCTTT	TTTTCCTTTC	TTTTTCCCTT	CTTTAATGGT	9500

FIG. 7E

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GGCTCCATCT	TAGCCCTAGT	CACGGCTAGC	TGTGAAAGGT	CCGTGAGCCG	9550
CATGACTGCA	GAGAGTGCTG	ATACTGGCCT	CTCTGCAGAT	CATGT	9595

FIG. 7F

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
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RCNLEDRDRS	ELSPLLLSTT	EWQILPCAFT	TLPALSTGLI	HLHQNIVDVQ	700
YLYGVGSAFV	SFAIKWEYIL	LLFLLLADAR	VCACLWMMLL	IAQAEAALEN	750
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FIG. 7G

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FIG. 7H

10/009002
JC13 Rec'd PCT/PTO 03 DEC 2001

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Arg Pro Arg Asn Tyr Lys Ile Ala Gly Ile His Asp Gly Leu Gln Thr
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Leu Ala Gln Ala Ala Leu Pro Ala His Gly Trp Gly Arg Gln Asp Pro
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Arg His Lys Ser Arg Asn Leu Gly Ile Leu Leu Asp Tyr Pro Leu Gly
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Trp Ile Gly Asp Val Thr Thr His Thr Pro Leu Val Gly Pro Leu Val
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Val Cys Leu Leu Ser Leu Ala Cys Pro Cys Ser Gly Ala Arg Val Thr
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Gln Val Ile Tyr Cys Ser Pro Ser Thr Cys Leu His Glu Pro Gly Cys
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Val Ile Cys Ala Asp Glu Cys Trp Val Pro Ala Asn Pro Tyr Ile Ser
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His Pro Ser Asn Trp Thr Gly Thr Asp Ser Phe Leu Ala Asp His Ile
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Asp Phe Val Met Gly Ala Leu Val Thr Cys Asp Ala Leu Asp Ile Gly
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Glu Leu Cys Gly Ala Cys Val Leu Val Gly Asp Trp Leu Val Arg His
245 250 255

Trp Leu Ile His Ile Asp Leu Asn Glu Thr Gly Thr Cys Tyr Leu Glu
260 265 270

Val Pro Thr Gly Ile Asp Pro Gly Phe Leu Gly Phe Ile Gly Trp Met
275 280 285

Ala Gly Lys Val Glu Ala Val Ile Phe Leu Thr Lys Leu Ala Ser Gln
290 295 300

Val Pro Tyr Ala Ile Ala Thr Met Phe Ser Ser Val His Tyr Leu Ala
305 310 315 320

Val Gly Ala Leu Ile Tyr Tyr Ala Ser Arg Gly Lys Trp Tyr Gln Leu
325 330 335

Leu Leu Ala Leu Met Leu Tyr Ile Glu Ala Thr Ser Gly Asn Pro Ile
340 345 350

Arg Val Pro Thr Gly Cys Ser Ile Ala Glu Phe Cys Ser Pro Leu Met
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Ile Pro Cys Pro Cys His Ser Tyr Leu Ser Glu Asn Val Ser Glu Val
370 375 380

Ile Cys Tyr Ser Pro Lys Trp Thr Arg Pro Ile Thr Leu Glu Tyr Asn
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Met Val Lys Phe Lys Asn Asn Thr Trp Gly Cys Cys Arg Ile Arg Asn
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Val Pro Ser Tyr Cys Thr Met Gly Thr Asp Ala Val Trp Asn Asp Thr
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Arg Asn Thr Tyr Glu Ala Cys Gly Val Thr Pro Trp Leu Thr Thr Ala
450 455 460

Trp His Asn Gly Ser Ala Leu Lys Leu Ala Ile Leu Gln Tyr Pro Gly
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Ser Lys Glu Met Phe Lys Pro His Asn Trp Met Ser Gly His Leu Tyr
485 490 495

Phe Glu Gly Ser Asp Thr Pro Ile Val Tyr Phe Tyr Asp Pro Val Asn
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Ser Thr Leu Leu Pro Pro Glu Arg Trp Ala Arg Leu Pro Gly Thr Pro
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Pro Val Val Arg Gly Ser Trp Leu Gln Val Pro Gln Gly Phe Tyr Ser
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Asp Val Lys Asp Leu Ala Thr Gly Leu Ile Thr Lys Asp Lys Ala Trp
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Lys Asn Tyr Gln Val Leu Tyr Ser Ala Thr Gly Ala Leu Ser Leu Thr
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Gly Val Thr Thr Lys Ala Val Val Leu Ile Leu Leu Gly Leu Cys Gly
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Ser Lys Tyr Leu Ile Leu Ala Tyr Leu Cys Tyr Leu Ser Leu Cys Phe
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Gly Arg Ala Ser Gly Tyr Pro Leu Arg Pro Val Leu Pro Ser Gln Ser
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Tyr Leu Gln Ala Gly Trp Asp Val Leu Ser Lys Ala Gln Val Ala Pro
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Phe Ala Leu Ile Phe Phe Ile Cys Cys Tyr Leu Arg Cys Arg Leu Arg
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Tyr Ala Ala Leu Leu Gly Phe Val Pro Met Ala Ala Gly Leu Pro Leu
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Thr Phe Phe Val Ala Ala Ala Ala Ala Gln Pro Asp Tyr Asp Trp Trp
675 680 685

Val Arg Leu Leu Val Ala Gly Leu Val Leu Trp Ala Gly Arg Asn Arg
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Gly His Arg Ile Ala Leu Leu Val Gly Pro Trp Pro Leu Val Ala Leu
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Leu Thr Leu Leu His Leu Val Thr Pro Ala Ser Ala Phe Asp Thr Glu
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Ile Ile Gly Gly Leu Thr Ile Pro Pro Val Val Ala Leu Val Val Met
740 745 750

Ser Arg Phe Gly Phe Phe Ala His Leu Leu Pro Arg Cys Ala Leu Val
755 760 765

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Asn Ser Tyr Leu Trp Gln Arg Trp Glu Asn Trp Phe Trp Asn Val Thr
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Leu Arg Pro Glu Arg Phe Phe Leu Val Leu Val Cys Phe Pro Gly Ala
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Thr Tyr Asp Ala Leu Val Thr Phe Cys Val Cys His Val Ala Leu Leu
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Cys Leu Thr Ser Ser Ala Ala Ser Phe Phe Gly Thr Asp Ser Arg Val
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Arg Ala His Arg Met Leu Val Arg Leu Gly Lys Cys His Ala Trp Tyr
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Ser His Tyr Val Leu Lys Phe Phe Leu Leu Val Phe Gly Glu Asn Gly
    850                 855                 860

Val Phe Phe Tyr Lys His Leu His Gly Asp Val Leu Pro Asn Asp Phe
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Ala Ser Lys Leu Pro Leu Gln Glu Pro Phe Phe Pro Phe Glu Gly Lys
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Ala Arg Val Tyr Arg Asn Glu Gly Arg Arg Leu Ala Cys Gly Asp Thr
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Val Asp Gly Leu Pro Val Val Ala Arg Leu Gly Asp Leu Val Phe Ala
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Gly Leu Ala Met Pro Pro Asp Gly Trp Ala Ile Thr Ala Pro Phe Thr
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Leu Gln Cys Leu Ser Glu Arg Gly Thr Leu Ser Ala Met Ala Val Val
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Met Thr Gly Ile Asp Pro Arg Thr Trp Thr Gly Thr Ile Phe Arg Leu
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Gly Ser Leu Ala Thr Ser Tyr Met Gly Phe Val Cys Asp Asn Val Leu
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Tyr Thr Ala His His Gly Ser Lys Gly Arg Arg Leu Ala His Pro Thr
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Gly Ser Ile His Pro Ile Thr Val Asp Ala Ala Asn Asp Gln Asp Ile
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Asp Glu Leu Ala Asn Glu Leu Ala Arg Lys Gly Ile Thr Ala Val Ser
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Tyr Tyr Arg Gly Cys Asp Ile Ser Lys Ile Pro Glu Gly Asp Cys Val
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Val Val Ala Thr Asp Ala Leu Cys Thr Gly Tyr Thr Gly Asp Phe Asp
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Ser Val Tyr Asp Cys Ser Leu Met Val Glu Gly Thr Cys His Val Asp
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Leu Asp Pro Thr Phe Thr Met Gly Val Arg Val Cys Gly Val Ser Ala
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Ile Val Lys Gly Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Ala Gly
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Ile Tyr Tyr Tyr Val Asp Gly Ser Cys Thr Pro Ser Gly Met Val Pro
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Glu Cys Asn Ile Val Glu Ala Phe Asp Ala Ala Lys Ala Trp Tyr Gly
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Leu Ser Ser Thr Glu Ala Gln Thr Ile Leu Asp Thr Tyr Arg Thr Gln
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Pro Gly Leu Pro Ala Ile Gly Ala Asn Leu Asp Glu Trp Ala Asp Leu
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Phe Ser Met Val Asn Pro Glu Pro Ser Phe Val Asn Thr Ala Lys Arg
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Thr Ala Asp Asn Tyr Val Leu Leu Thr Ala Ala Gln Leu Gln Leu Cys
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His Gln Tyr Gly Tyr Ala Ala Pro Asn Asp Ala Pro Arg Trp Gln Gly
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Ala Arg Leu Gly Lys Lys Pro Cys Gly Val Leu Trp Arg Leu Asp Gly
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Tyr Gln Pro Pro Cys Gly Ala Gly Ser Leu Thr Arg Cys Ser Cys Gly
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Glu Thr Lys Gly Tyr Leu Val Thr Arg Leu Gly Ser Leu Val Glu Val
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Asn Lys Ser Asp Asp Pro Tyr Trp Cys Val Cys Gly Ala Leu Pro Met
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Ala Val Ala Lys Gly Ser Ser Gly Ala Pro Ile Leu Cys Ser Ser Gly
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His Val Ile Gly Met Phe Thr Ala Ala Arg Asn Ser Gly Gly Ser Val
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Ser Gln Ile Arg Val Arg Pro Leu Val Cys Ala Gly Tyr His Pro Gln
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Tyr Thr Ala His Ala Thr Leu Asp Thr Lys Pro Thr Val Pro Asn Glu
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Tyr Ser Val Gln Ile Leu Ile Ala Pro Thr Gly Ser Gly Lys Ser Thr
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Lys Leu Pro Leu Ser Tyr Met Gln Glu Lys Tyr Glu Val Leu Val Leu
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Asn Pro Ser Val Ala Thr Thr Ala Ser Met Pro Lys Tyr Met His Ala
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Thr Gly Ala Ser Leu Thr Tyr Ser Thr Tyr Gly Met Tyr Leu Thr Gly
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Thr Asp Ala Thr Thr Val Leu Gly Ile Gly Lys Val Leu Thr Glu Ala
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Pro Ser Lys Asn Val Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro
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Ser Cys Val Phe Ala Phe Ile Ala Gly Ile Thr Thr Pro Leu Pro His
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Lys Ile Lys Met Phe Leu Ser Leu Phe Gly Gly Ala Ile Ala Ser Lys
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Leu Thr Asp Ala Arg Gly Ala Leu Ala Phe Met Met Ala Gly Ala Ala
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Gly Thr Ala Leu Gly Thr Trp Thr Ser Val Gly Phe Val Phe Asp Met
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Leu Gly Gly Tyr Ala Ala Ala Ser Ser Thr Ala Cys Leu Thr Phe Lys
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Cys Leu Met Gly Glu Trp Pro Thr Met Asp Gln Leu Ala Gly Leu Val
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Tyr Ser Ala Phe Asn Pro Ala Ala Gly Val Val Gly Val Leu Ser Ala
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Cys Ala Met Phe Ala Leu Thr Thr Ala Gly Pro Asp His Trp Pro Asn
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Arg Leu Leu Thr Met Leu Ala Arg Ser Asn Thr Val Cys Asn Glu Tyr
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Phe Ile Ala Thr Arg Asp Ile Arg Arg Lys Ile Leu Gly Ile Leu Glu
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Ala Ser Thr Pro Trp Ser Val Ile Ser Ala Cys Ile Arg Trp Leu His
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Thr Pro Thr Glu Asp Asp Cys Gly Leu Ile Ala Trp Gly Leu Glu Ile
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Trp Gln Tyr Val Cys Asn Phe Phe Val Ile Cys Phe Asn Val Leu Lys
1875 1880 1885

Ala Gly Val Gln Ser Met Val Asn Ile Pro Gly Cys Pro Phe Tyr Ser
1890 1895 1900

Cys Gln Lys Gly Tyr Lys Gly Pro Trp Ile Gly Ser Gly Met Leu Gln
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Ala Arg Cys Pro Cys Gly Ala Glu Leu Ile Phe Ser Val Glu Asn Gly
1925 1930 1935

Phe Ala Lys Leu Tyr Lys Gly Pro Arg Thr Cys Ser Asn Tyr Trp Arg
1940 1945 1950

Gly Ala Val Pro Val Asn Ala Arg Leu Cys Gly Ser Ala Arg Pro Asp
1955 1960 1965

Pro Thr Asp Trp Thr Ser Leu Val Val Asn Tyr Gly Val Arg Asp Tyr
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Cys Lys Tyr Glu Lys Met Gly Asp His Ile Phe Val Thr Ala Val Ser
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2005 2010 2015

Val Ala Val Asp Gly Val Gln Val Gln Cys Tyr Leu Gly Glu Pro Lys
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Lys Thr Val Lys Leu Pro Phe Arg Val Asp Gly His Thr Pro Gly Val
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Arg Met Gln Leu Asn Leu Arg Asp Ala Leu Glu Thr Asn Asp Cys Asn
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Pro Pro Pro Pro Arg Ser Val Pro Gly Val Ser Cys Pro Glu Ser Leu
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Gly Pro Asp Asp Leu Pro Ser Tyr Pro Pro Lys Lys Glu Val Ser Glu
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2275 2280 2285

Ala Ser Lys Val Leu Ser Ala Thr Arg Ala Ile Thr Ser Gly Phe Leu
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Lys Gln Arg Ser Leu Val Tyr Val Thr Glu Pro Arg Asp Ala Glu Leu
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Arg Lys Gln Lys Val Thr Ile Asn Arg Gln Pro Leu Phe Pro Pro Ser
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Tyr His Lys Gln Val Arg Leu Ala Lys Glu Lys Ala Ser Lys Val Val
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Gly Val Met Trp Asp Tyr Asp Glu Val Ala Ala His Thr Pro Ser Lys
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Ser Ala Lys Ser His Ile Thr Gly Leu Arg Gly Thr Asp Val Arg Ser
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Gly Ala Ala Arg Lys Ala Val Leu Asp Leu Gln Lys Cys Val Glu Ala
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Gly Glu Ile Pro Ser His Tyr Arg Gln Thr Val Ile Val Pro Lys Glu
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Glu Val Phe Val Lys Thr Pro Gln Lys Pro Thr Lys Lys Pro Pro Arg
2420 2425 2430

Leu Ile Ser Tyr Pro His Leu Glu Met Arg Cys Val Glu Lys Met Tyr
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Tyr Gly Gln Val Ala Pro Asp Val Val Lys Ala Val Met Gly Asp Ala
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/15293

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/51 C07K14/18 C12Q1/68 C12N7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 21922 A (PILOT MATIAS TAMI J ;BUIJK SHERI L (US); SIMONS JOHN N (US); ABBOT) 17 August 1995 (1995-08-17) page 4, line 18 -page 6, line 17 page 55, line 24 -page 56, line 19 page 76; example 5 page 89, line 18 -page 96 page 109; example 15 page 148; example 21 page 427, line 17 -page 432 claims ---	1,2,4-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2000	31/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Andres, S

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SCARSELLI ELISA ET AL: "GB virus B and hepatitis C virus NS3 serine proteases share substrate specificity." JOURNAL OF VIROLOGY, vol. 71, no. 7, July 1997 (1997-07), pages 4985-4989, XP002150190 ISSN: 0022-538X cited in the application the whole document ---	19,24-26
A	HONDA MASAO ET AL: "A phylogenetically conserved stem-loop structure at the 5' border of the internal ribosome entry site of hepatitis C virus is required for cap-independent viral translation." JOURNAL OF VIROLOGY, vol. 73, no. 2, February 1999 (1999-02), pages 1165-1174, XP002150191 ISSN: 0022-538X cited in the application the whole document ---	19,22,23
A	YANAGI MASAYUKI ET AL: "In vivo analysis of the 3' untranslated region of the hepatitis C virus after in vitro mutagenesis of an infectious cDNA clone." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 5, 2 March 1999 (1999-03-02), pages 2291-2295, XP002150192 ISSN: 0027-8424 cited in the application ---	
A	YANAGI M ET AL: "Transcripts of a chimeric cDNA clone of hepatitis C virus genotype 1b are infectious in vivo" VIROLOGY, vol. 244, no. 1, 1998, pages 161-172, XP002089701 ISSN: 0042-6822 cited in the application ---	
P,X	BUKH JENS ET AL: "Toward a surrogate model for hepatitis C virus: An infectious molecular clone of the GB virus-B hepatitis agent." VIROLOGY, vol. 262, no. 2, 30 September 1999 (1999-09-30), pages 470-478, XP002150193 ISSN: 0042-6822 the whole document ---	1-16,19

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1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	SBARDELLATI ANDREA ET AL: "Identification of a novel sequence at the 3' end of the GB virus B genome." JOURNAL OF VIROLOGY, vol. 73, no. 12, December 1999 (1999-12), pages 10546-10550, XP002150194 ISSN: 0022-538X the whole document	1-16,19
P,X	BUTKIEWICZ N. ET AL.: "Virus-specific cofactor requirement and chimeric hepatitis C virus/GB virus B nonstructural protein 3." J VIROL 2000 MAY;74(9):4291-301, XP002150195 the whole document	19, 24-26, 33-35, 37,39

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INTERNAT[redacted]NAL SEARCH REPORT

I. [redacted]n on patent family members

Int[redacted]al Application No
P[redacted]US 00/15293

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521922 A	17-08-1995	CA 2166313 A	17-08-1995
		EP 0745129 A	04-12-1996
		JP 10337193 A	22-12-1998
		JP 9511137 T	11-11-1997
		US 5981172 A	09-11-1999
		US 5843450 A	01-12-1998
		US 6051374 A	18-04-2000
		WO 9829747 A	09-07-1998